Depression in Multiple Sclerosis: Prevalence, Profile and Treatment

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2017

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This thesis was prepared at the Department of Research & Innovation of GGZ inGeest, and the Department of Psychiatry, VU University Medical Center, Amsterdam, within the EMGO+ Institute for Health and Care Research. The research described in this thesis was financially supported by Stichting MS Research (grant number 08-651 & 09-678), Stichting tot Steun VCVGZ (grant number ST2688.Me3), and Fonds NutsOhra (grant number 0904-58). The infrastructure for the NESDA study (www.nesda.nl) has been funded through the Geestkracht program of the Netherlands Organisation for Health Research and Development (Zon-Mw, grant number 10-000-1002) and participating universities (VU University Medical Center, Leiden University Medical Center, University Medical Center Groningen).

Financial support for publication and distribution of this thesis was kindly provided by the Department of Psychiatry, VU University Medical Center & VU University Amsterdam; Minddistrict; and Stichting MS Research.

ISBN: 978-94-028-0474-4

Cover design: sophie ontwerpt//
Lay-out: Joska Sesink, persoonlijkproefschrift.nl
Printing: Ipskamp Printing, Enschede, The Netherlands

VRIJE UNIVERSITEIT

Depression in Multiple Sclerosis: Prevalence, Profile and Treatment

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad Doctor aan
de Vrije Universiteit Amsterdam,
op gezag van de rector magnificus
prof.dr. V. Subramaniam,
in het openbaar te verdedigen
ten overstaan van de promotiecommissie
van de Faculteit der Geneeskunde
op vrijdag 3 februari 2017 om 11.45 uur
in de aula van de universiteit,
De Boelelaan 1105

door

Rosa Elisabeth Boeschoten

geboren te Hilversum

promotoren:	prof.dr. P.C. van Oppen
	prof.dr. B.M.J. Uitdehaag
copromotoren:	prof.dr. J. Dekker
	prof.dr. A.T.F. Beekman

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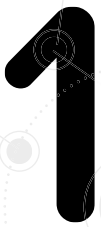

GENERAL INTRODUCTION

Symptoms of depression have been considered characteristic of Multiple Sclerosis (MS) from the moment the first descriptions of the disease were made in the late nineteenth hundred. In his *Lectures on the Diseases of the Nervous System,* the French neurologist Charcot noted how mood disturbances were a common feature among people suffering from MS: "it is not rare to see them…melt into tears without reason" [1]–[3] (Charcot 1879, cited by Minden & Schiffer, 1993). But despite extensive research on neurological manifestations of MS, depression in MS did not get a front-row seat until the 1950s [4]. Today, comorbid depressive symptomatology in MS is an important topic of research, and numerous studies demonstrated close links, high prevalence and negative consequences. That said, research on this subject is not comprehensive and depression in MS patients often remains undetected and inadequately treated [5].

This chapter first introduces general background and existing literature on depression in MS. It then elaborates on remaining research gaps and possibilities to improve the quality of care for depressed MS patients, closing with the aims of this thesis. This thesis focusses on the 1) prevalence of depression in established MS populations, 2) clinical symptom profile of depression in MS patients with overlapping psychiatric and neurological symptoms, and 3) feasibility and effectiveness of online delivered psychotherapy for clinically relevant depression in MS.

MULTIPLE SCLEROSIS

Multiple Sclerosis (MS) is a chronic and progressive inflammatory and degenerative disease of the central nervous system (CNS). MS is about twice as common in women as in men and affects around 2,5 million individuals worldwide [6]. In the Netherlands, approximately 1 in 1000 persons are diagnosed with MS [7]. MS aetiology is not fully understood, but a complex interplay between genetic and environmental factors is suggested to play a role in MS development [6],[8].

MS is characterized by CNS inflammation and by damage of axons and myelin sheaths that insulate the nerve fibers. These changes disrupt neural transmissions, causing in turn neurological symptoms such as loss of limb function or feeling, poor balance, vision problems, fatigue, spasticity, loss of control over bladder and bowel, sexual dysfunction, impaired speech, pain or cognitive impairment [6],[8].

Clinical manifestations and course of MS are highly variable and difficult to predict, but most MS patients will accumulate disability over time [9]. The majority of MS patients initially experience a relapsing remitting disease course (RRMS). RRMS is characterized by exacerbations, attacks of new or increasing neurological symptoms, followed by partial or complete recovery. But for most patients, recovery is temporary. Around 80% of RRMS patients transits to a secondary progressive course of MS (SPMS), with progressive loss of neurologic function over time. In 20% of the patients, MS progresses without early relapses or remissions from the first onset of symptoms. Patients are expected to live at least 25 years from disease onset, and most die from unrelated causes [6].

The diagnosis of MS is based on clinical findings and/or on demonstration of MS-typical white matter lesions throughout the CNS disseminated in space and time (>1 region in the CNS, >1

disease event) using magnetic resonance imaging (MRI) [8]. New diagnostic criteria for MS, the so called McDonald criteria, were established in 2001 and revised in 2005 and 2010 [10]. Although a curative treatment for MS does not exist yet, medication treatment is able to reduce the number and severity of exacerbations, prevent and treat disability through progression, and relief MS symptoms [6].

Onset of MS mainly occurs in early to middle adult life (20-40 years) [8], a critical time in which most people start families and establish careers. MS diagnosis and its uncertain and progressive nature can have a major impact on several key areas of functioning. MS patients are confronted with a grim prognosis, reduced physical functioning, and unpredictability of everyday health being part of MS. In addition they could face many other problems such as difficulty performing usual responsibilities, significant disruption in employment and family functioning, loss of social support, and financial problems. To maintain an optimistic view about the future can therefore be a major challenge [11]–[14].

DEPRESSION

Comorbidity of depression is common in the MS population and has since long been acknowledged to be of a concern [11]. A depressive disorder is a heterogeneous syndrome that can manifest itself in different ways. A diagnosis of major depressive disorder (MDD) involves a 1) depressed mood and/or 2) markedly diminished interest of pleasure in all or most activities, most of the day and nearly every day during at least 2-weeks. Together with one or two core symptoms, five or more additional symptoms should be present during at least a 2-week period such as fatigue or loss of energy, insomnia or hypersomnia, psychomotor agitation or retardation, decreased or increased appetite, significant weight loss or gain, feelings of worthlessness or inappropriate quilt, indecisiveness, difficulty to think or concentrate, or suicidal ideation. In addition, depression can appear in minor or subthreshold forms, also characterized by a collection of cognitive, affective and somatic depressive symptoms with more symptoms indicating more marked depression. Depression aetiology remains unclear but a combination of genetic, chemical, biological, psychological, social and environmental factors is likely to contribute to its presence [15].

Depression is known as an important world-wide health problem and a major contributor to overall global burden of disease [16]. Impaired functioning is greatly increased when a depressive disorder is accompanied by a physical illness [17]. In MS, depression may influence the disease process negatively and impedes coping with disability [14]. In addition, depression in MS is associated with fatigue, a cutback in working hours, cognitive impairment, and poorer social support [18]. Moreover, it is related to lower quality of life [19], and increased risk of suicide [20]. Depression and anxiety often co-occur, which has been associated with worse clinical outcomes than in depression alone [21],[22].

There is growing evidence that depression is more common in patients with a physical (chronic) illness [17]. Also in MS patients, the prevalence of depression is suggested to be substantially higher compared with the general population [11].

DEPRESSION IN MS

Increased risk

Although increased risk of depression in case of MS has been established, reported prevalence rates vary widely (14%-54%) [5],[23]. Variation could be due to a number of methodological issues [24], such as the size and nature of the studied population and wide variety of definitions, instruments and diagnostic criteria used to diagnose and quantify depression in MS. Examined patients often represent small samples attending MS-clinics or inpatient settings, underrepresenting patients coping well in the community [22],[25],[26]. In addition, in most MS literature the term 'depression' refers to clinically significant symptoms revealed by self-report scales of different quality, making it difficult to compare findings [5],[27]. Besides, these scales cannot be used to establish a formal diagnosis of depressive disorders and tend to overestimate prevalence rates as compared with diagnostic interviews [24],[28] that are used far less frequently. Clearly, there is a need for a more comprehensive understanding of comorbid symptoms and disorders of depression in MS. Therefore, the first aim of this thesis is to systematically review the scientific literature and estimate the average depression prevalence in MS taking into account different population settings, definitions and diagnostic approaches. To avoid confusion in terminology, as now often is the case in MS literature, the term 'depression' will reflect both clinically relevant symptoms and disorders in this chapter, unless noted otherwise.

Aetiology

Elevated prevalence rates of depression in MS could have multiple causes, including psychological, social, neurobiological, immunologic, and genetic factors [14],[29]. It remains unclear to what degree depression in MS is primarily a reaction to the presence of a chronic medical condition with an uncertain and unpredictable course, or a neurological consequence of MS-related neurobiological aetiology [14].

Psychosocial factors as low social support, occupational problems, or maladaptive coping style are known to be associated with depression in MS [11],[13],[18]. In addition, MS-related cognitive deficits or fatigue are believed to increase vulnerability to depression [11],[22]. There is no clear association between the presence of depression and disease related variables such as physical disability, disease course and duration, which is attributed to the diversity of MS itself [30]. MS-related disease processes such as structural brain changes, elevated Hypothalamic-Pituitary-Adrenal (HPA)-axis activity and immune-inflammatory dysregulations were found to be related to presence and severity of depression in MS [31]–[33], but a thorough understanding of the associations between neurobiological pathology and depressive symptoms is still lacking. It is beyond the scope of this thesis to unravel various aetiological underpinnings of MS-related depression that seem to concern many psychosocial and biological factors. It should be clear however that psychosocial and biological theories can be viewed as complementary rather than mutually exclusive [22].

RECOGNITION

Clinical profile of MS-related depression

Confounding of depression and illness at symptomatic level is known to be an important methodological issue in depression research in neurodegenerative disorders such as MS, Parkinson's disease, Alzheimer's, Huntington disease and amyotrophic lateral sclerosis. Due to shared symptom profiles it is challenging to clinically evaluate depressive symptoms in these diseases. In MS, overlapping psychiatric and neurological symptoms such as fatigue, psychomotor slowing, concentration and sleeping problems could indicate that depression can be both a complication in addition to MS, as well a symptom of MS [13]. As a result, misunderstanding of MS-related symptoms as depression may lead to unnecessary treatment, whereas failure to recognize an underlying depressive disorder can hamper sufficient care. Disentangling overlapping symptoms is suggested to be a substantial difficulty and often becomes an aetiological puzzle [22]. In addition, it is suggested meaningless to force these overlapping symptoms into either psychiatric or neurologic grouping since psychiatric disorders are disorders of the brain and therefore neurological at least at one level of understanding [34]. According to experienced clinicians, neuropsychiatric symptoms of depression such as fatigue or psychomotor slowing can be distinguished from MS associated symptoms during a clinical interview [11]. It gets more complicated when depression is determined by commonly used self-report scales which often confound these symptoms.

There is no consensus yet among researchers as to a gold standard to clinically assess and recognize depression in MS patients [5]. In addition, research concerning the clinical profile of MS-related depression is still scarce. MS symptoms or a direct MS-related pathophysiological aetiology may play an important role in the expression of depression in MS patients, and influence its clinical phenotype. They may inflate the number of somatic symptoms and increase estimates of depression. Furthermore, abnormalities in both the limbic and endocrine system of MS patients may be more closely related to affective and cognitive depressive symptoms in MS [31],[33] whereas MS-inflammatory markers showed stronger correlations with neurovegetative symptoms [32],[33]. Other research suggests depressed MS patients to typically express symptoms of angriness, irritability, worries and discouragement. Symptoms as 'guilt', 'worthlessness', 'withdrawal' and 'apathy' are to a lesser extend observed in patients with comorbid depressive symptoms and MS as in those with primary depression [3],[35]. One study found depressed and non-depressed MS patients to be best differentiated by symptoms of 'sadness', 'pessimism', 'sense of failure', 'guilt', 'disappointment', and 'changes in appetite and/or weight' [36]. However, a recent study showed depressive symptoms to be similar in MS patients with moderate or severe depressive symptoms compared with MDD patients without MS [37].

It remains unclear whether the clinical profile of major depressive disorder remains valid among MS patients as earlier conclusions have been inconsistent and are based on small samples and self-reported depression. The second aim of this thesis is therefore to investigate the depressive symptom profile in a larger representative MS sample with a clinical diagnosis of

MDD. This can be considered a subsequent step to substantiate how the depression concept in MS should be defined in order to improve recognition and assessment.

Screening

Depression in MS is often not recognized [20],[26] and more than half of the cases of depression in MS patients are thought to stay undiagnosed [38],[39]. Explanations are numerous. As noted above, overlapping symptoms might be entirely ascribed to MS when in fact a portion of those symptoms is attributable to depression. In addition, patients can feel resistance to disclose their emotional problems or perceive them as an unsolvable component of the disease, therefore leaving them unmentioned [11]. Further, it is suggested that MS patients are not actively screened and diagnosed by their clinician on depression, as mental problems are not the primary focus of consults [40]. However, depression in MS does not seem to remit spontaneously and may even worsen over time if not treated [40], emphasising the relevance of early detection.

It was recommended that, with each visit to the neurologist or clinic, MS nurses should screen and evaluate the level of distress in MS patients [41]. Regular screening offers possibilities to identify and rapidly refer depressed and/or impaired patients to appropriate care and monitor complaints. Also, screening can increase patient's awareness of experienced distress such as depressive symptoms, which might decrease barriers to request appropriate treatment. Lately, successful initiatives of computer-assisted screening in health care have grown. Advantages are high compliance rates, rapid completion and processing, and directly available results [42]–[46]. Whether a computer-based screening method that can be easily incorporated into clinical-care is a feasibly method to support MS nurses in identifying psychological needs of MS patients, is still a field to explore and is addressed in this thesis.

TREATMENT OF DEPRESSION IN MS

Effective treatments

There are several effective treatments for depression in general, including different forms of pharmacotherapy and psychological treatments [47],[48]. Given the evidence for these treatments in depressed patients without MS, pharmacotherapy and psychological therapies are often used to treat depression in MS patients although evidence for this particular patient group is scarce [5].

There is some support for efficacy of pharmacologic therapies for depression in MS patients. Next to medication treatment, depressed MS patients seem to respond well to psychological treatments [5],[23],[49]. This especially applies to cognitive behaviour therapy (CBT) that focuses on developing skills to cope with emotions, thoughts, and adjustment to the unpredictable and uncertain course of MS and its consequences [12],[40]. Still, the value of CBT in treating depressed MS patients has been examined to a limited extent.

In addition, although MS patients seem to benefit from depression treatment [11],[23],[49], they often do not receive appropriate care [5],[39]. The proportion of depressed MS patients reporting treatment for depression is surprisingly low and many patients with clinical significant

depressive symptoms report unmet needs for medication or psychotherapy treatment [50],[51]. MS patients may experience additional difficulties in attending psychotherapy treatment due to disease-related barriers such as transportation difficulties, physical immobility, fatigue and MS exacerbations [13]. These complicating factors can have a major impact on receiving face-to-face treatment [49],[52]. Consequently, many depressed MS patients are still insufficiently treated.

Internet-based treatment

Alternative psychotherapy treatment delivery such as brief sessions, therapy by telephone or more self-help orientated alternatives should be considered to increase access to mental health care for depressed MS patients. Telephone administered CBT has previously shown to be more effective in reducing depressive symptoms in MS patients compared with MS patients receiving supportive emotion-focused therapy [52] or no mental health care at all [53].

In addition, the Internet has grown as an important tool for delivering mental health interventions. Internet-based CBT (ICBT) was reported to be as effective as face-to-face therapy [54] and a successful method of treatment for depression in general [55],[56]. Internet-based treatment is easily accessible, cost-effective and can reach a large number of people with functional impairments due to physical health problems. These advantages make it an attractive treatment for the MS population. Although ICBT can be effective in reducing depressive symptoms in the general population and in patients with a medical condition [57], evidence is lacking whether it can be a feasible and effective treatment for depressive symptoms in MS patients (Third thesis aim). If so, online treatment offers possibilities to reach a group of underserved depressed MS patients who may experience disease-related barriers to participate in face to-face counselling.

AIMS AND OUTLINE OF THIS THESIS

The general objective of this thesis is to gain more insight in MS-related depression and its treatment in order to improve quality of care for depressed MS patients. In order to do so, the first aim is to examine the prevalence of depressive symptoms and depressive disorder in MS, taking into account different population settings and diagnostic approaches. The second aim is to investigate the clinical profile of MS-related MDD to improve recognition and selection of adequate treatment. The third aim is to explore screening and treatment alternatives using recent computer-based technological developments, and examine the effectiveness of an Internet-based CBT intervention for clinically relevant depressive symptoms in MS. Since depression and anxiety often co-occur, the prevalence of anxiety and its comorbidity to depression in MS is additionally assessed throughout this thesis.

In line with our aims, **Chapter 2** presents a systematic review and meta-analysis with a targeted analysis of studies on prevalence of depression and anxiety in MS in which 1) prevalence of depression and anxiety in MS is estimated and 2) sources of heterogeneity are explored by discussing the selected studies in-depth (assessment method, prevalence period, study quality, recruitment resource, region). Whether the clinical profile of MDD remains valid among MS

patients is discussed in **Chapter 3**. **Chapter 4** contains a feasibility study of a computer-based screening method to identifying psychological needs of MS patients. **Chapter 5** presents a pilot study on the feasibility and outcome of ICBT as an alternative treatment opportunity to reduce depressive symptoms in MS patients. The tested intervention concerns a guided Internet-based self-help problem solving therapy (IPST) which is a form of CBT with a focus on developing sufficient coping skills [58]. In **Chapter 6** the study protocol of the randomized controlled trial that we conducted to investigate effectiveness of IPST for depression is provided in order to enhance methodological clarity and further research. The results of this trial are presented in **Chapter 7**. Finally, the main findings of chapter 2 to 7 are summarized and discussed in **Chapter 8**.

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2

PREVALENCE OF DEPRESSION AND ANXIETY IN MULTIPLE SCLEROSIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Journal of the Neurological Sciences. 2017; 372:331–341.

ABSTRACT

Objective: Prevalence rates of depression and anxiety in patients with Multiple Sclerosis (MS) vary widely across studies. Aim of this systematic review and meta-analysis was to a) estimate the prevalence of depression and anxiety in MS, and specifically b) explore sources of heteroge neity (assessment method, prevalence period, study quality, recruitment resource, region) by extensive analyses.

Methods: A computerized search in PubMed, EMBASE, and PsycINFO for studies on depression and anxiety in MS was performed up to December 2014.

Results: Fifty-eight articles with a total sample size of 87,756 MS patients were selected. Pooled mean prevalence was 30.5% (95%CI=26.3%–35.1%) for depression, and 22.1% (95%CI=15.2%–31.0%) for anxiety. Prevalence of clinically significant depressive or anxiety symptoms was higher (35% and 34%) compared with disorders (21%, p=.001 and 10%, p<.001). Prevalence of a depressive disorder was relatively lower in studies from Europe. Anxiety disorder was more prevalent in community-based samples. Sources of high heterogeneity were not revealed.

Conclusions: Data of a large number of patients indicate increased prevalence of depression and anxiety in MS. Further research is needed to identify sources of heterogeneity. Issues to consider are the definition of depression and anxiety, patient recruitment, and patient characteristics.

INTRODUCTION

Depression and anxiety are common in Multiple Sclerosis (MS) and elevated compared with the general population [1]. Explanations for comorbidity are multifactorial and concern a complex interplay of variables. Depression and anxiety could be natural reactions to the unpredictable course of a disabling and chronic disease. Further, MS patients could be predisposed for depression or anxiety by several psychosocial risk factors such as inadequate coping or insufficient social support, or by MS-related biological processes such as changes in brain structure or in immunological and inflammatory pathways [2]–[5]. In reverse, depression and anxiety may adversely affect health status by increasing symptom burden, negatively influencing adherence to treatment regimens or by direct pathophysiological effects on immunity [6],[7]. Depression and anxiety in MS patients are related to lower quality of life, cognitive dysfunction, elevated suicide risk, and working problems [4],[8]. Since depression and anxiety in MS seem to worsen over time and as they are often treatable, early recognition is important and knowledge on their presence and management should be further improved in order to enhance clinical care [4],[9]–[11].

The increased risk of depression or anxiety in MS has often been reported but prevalence rates vary widely from 14% up to 54% [9],[12]. This variation could be due to a number of methodological issues, such as differences in definitions, instruments and diagnostic criteria used, and size and nature of the population studied [13]. Often the terms 'depression' and 'anxiety' refer to clinically significant symptoms revealed by self-report scales of different quality, which makes it difficult to compare findings [9],[14]. Besides, these scales cannot be used to establish a formal diagnosis of psychiatric disorders and tend to overestimate prevalence rates as compared with diagnostic interviews [13],[15]. Further, depressive and anxiety symptomatology in MS has frequently been studied in small MS samples attending MS-clinics or in inpatient settings, underrepresenting patients who are coping well in the community [1],[16],[17].

A systematic review pooling data from population-based studies showed that depression and anxiety both affect more than 20% of the MS population [14]. Although the authors performed sensitivity analyses and focused on high quality studies, a high degree of heterogeneity was observed. This implied that prevalence rates varied considerably between the included studies, hampering solid conclusions for the MS population. It is therefore clearly of interest to determine the causes of this heterogeneity as is also suggested by the Cochrane Handbook [18]. This has, to the best of our knowledge, not been previously performed. In addition to revealing the sources of heterogeneity and improving prevalence estimates, it might also offer explanations for the elevated prevalence rates in MS.

In this systematic review and meta-analysis, we therefore aimed to provide a targeted analysis of studies on the prevalence of depression and anxiety in MS and 1) estimate the prevalence of depression and anxiety in MS, and in addition 2) explore sources of heterogeneity by performing subgroup analyses. We evaluated whether the average prevalence estimates varied in relation to a) different definitions of depression and anxiety (disorder versus clinically significant symptoms), b) various methods of assessment and prevalence period, c) quality of research papers, d) patient recruitment resources, and e) different regions. By exploring the heterogeneity by conducting

subgroup analyses, we strived to obtain a more comprehensive view on the prevalence of depression and anxiety in MS and its implications for future research.

MATERIALS AND METHODS

Search strategy

A systematic computerized search in PubMed, EMBASE, and Psycinfo was completed in December 2014 for studies on depression and anxiety in Multiple Sclerosis. In collaboration with the librarian, a search strategy was developed which was adjusted correspondingly for each of the databases: The medical subject headings (MeSH) terms 'Depression', 'Depressive Disorder', 'Depressive', 'Anxiety', 'Anxiety Disorders', 'Anxious', 'Emotions', 'Affective Symptoms', 'Mood Disorders', 'Distress', 'Psychological', 'Mental', 'Neurotic' were combined with 'Multiple Sclerosis' and with 'Epidemiology', 'Epidemiologic Studies', and 'Prevalence'. The search was supplemented with a free text word search of these terms (electronic search strategy is displayed in supplementary material A).

Inclusion and exclusion criteria

Studies were included if they met the following criteria: 1) full text publication in English in a peer reviewed journal, 2) a sample size of ≥200 of outpatients with an MS diagnosis, either by self-report or by clinician, 3) report of a depressive or anxiety disorder somewhere during the course of MS by a clinician, identified with (semi) structured interviews based on the Diagnostic and Statistical Manual of Mental disorders (DSM III/IV) [19], the International Classification of Diseases (ICD-9/10) [20] or the International Classification of Primary Care (ICPC) [21] on depressive or anxiety disorders, or clinically significant depressive or anxiety symptoms identified with self-report questionnaires with appropriate psychometric quality (no sub-scales or self-report diagnosis), and 4) provision of sufficient information to calculate prevalence rates e.g. sample size and number or percentages of depressed or anxious patients. We excluded studies with errors in the calculation or presented results, patients under the age of 16 years, studies merely including patients with Clinical Isolated Syndrome or inpatients, and studies with epidemiologically selective samples such as case report studies, randomized controlled trials, reviews, and case-control studies without a general MS population.

Selection process

After duplicate publications were excluded, the first author (RB) screened all remaining abstracts on selection criteria. In case of indistinctness, full texts were consulted. Reference lists of the selected articles were checked to identify further articles. Subsequently, the selected articles were read in full text and rated on quality by two independent reviewers (RB and AB). Disagreements between the raters were discussed and resolved during consensus meetings.

During the selection process it turned out that several publications stemmed from the same study, which would lead to a disproportional influence on the calculated prevalence rate. In these cases, only the most recent publication with the highest sample size was included. Sample size

was given priority to publication year. Unselected articles [22]–[34] were still used to complete missing information on characteristics of the study design, MS, depression and anxiety. The only study on the prevalence of a post-traumatic stress disorder [35] (5.17%) was excluded, since all other studies regarding anxiety disorder focused on overall anxiety.

Quality assessment

The methodological quality of the selected studies was assessed using a 10-item checklist of quality criteria of Hoy *et al.* (2012) [36] that was developed to assess risk of bias in prevalence studies. The first four items of the checklist assess the external validity such as selection and non-response bias. Item 5 to 10 assess internal validity, e.g. measurement bias and bias related to analysis. Response options for individual items are low or high risk of bias. In case there was insufficient information in the article to permit a judgment for a particular item, we rated the item with a high risk of bias. Response options for the summary item on the overall risk of study bias are low, moderate, or high risk of bias. This is based on the rater's subjective judgment given responses to the preceding 10 items (see supplementary material B for more extensive information).

Data extraction

Study design, region, selection method, assessment time, and the demographic variables gender, age, method for assessing a diagnosis of MS, MS type, onset, and severity, as well as information on assessment method and prevalence period of anxiety and depression were extracted from each included article and rechecked by the first author. Two reviewers (RB and AB) independently extracted prevalence data from each study and consensus was reached by discussion.

Statistical analysis

The outcome consisted of descriptive data presented as pooled mean prevalence with 95% confidence intervals (95%CI). For studies that assessed disorders, this weighted prevalence equals the presence of a disorder as reflected by the number of patients. For studies using cut-off scores on depression and anxiety symptom rating scales, this percentage represents the presence of clinical significant symptoms as reflected by the number of patients scoring above the cut-off that was defined per study. When studies used more than one cut-off score to measure clinically significant symptoms, the percentage above the lowest clinically relevant cut-off score was recorded. In studies that investigated effects of Interferon Beta treatment, or brain imaging research, or in studies with follow up assessments, the baseline assessment was used for analyses. As we expected heterogeneity (the lack of consistency between results of studies) to be high, our analyses were performed using a random effects model. Heterogeneity was examined using the I^2-statistic; a value of 25% indicates low, 50% moderate and 75% indicates high heterogeneity [37]. In order to explore sources of heterogeneity, we conducted additional analyses for more homogeneous subgroups. When a minimum of two studies per subgroup was available, (comparative) analyses were performed for the following subgroups: disorder and clinically significant symptoms, method of assessment, prevalence period, quality of research paper, recruitment resource, and region. Z-tests were used to compare the prevalence in two

subgroups. For more than 2 subgroups a Q-test based on analyses of variance was used [38]. A *p*-value <.05 was considered significant. All analyses were performed with the computer program 'comprehensive meta-analysis' (CMA, version 2).

RESULTS

The literature search identified 2,999 articles published between August 1965 and December 2014. Examination of titles and abstracts resulted in 112 publications that were considered for inclusion. After full-text assessment, 58 articles met the inclusion criteria and were included in this review with a total sample size of 87,756 MS patients [11],[17],[28],[39]–[93]. Figure 2.1 shows the article extraction process.

Studies on depression meeting our selection criteria (*n*=58) outnumbered the studies on anxiety (*n*=15). Studies exclusively focusing on anxiety were absent. Characteristics of the study designs, and prevalence data per study and additional information on MS are displayed in the

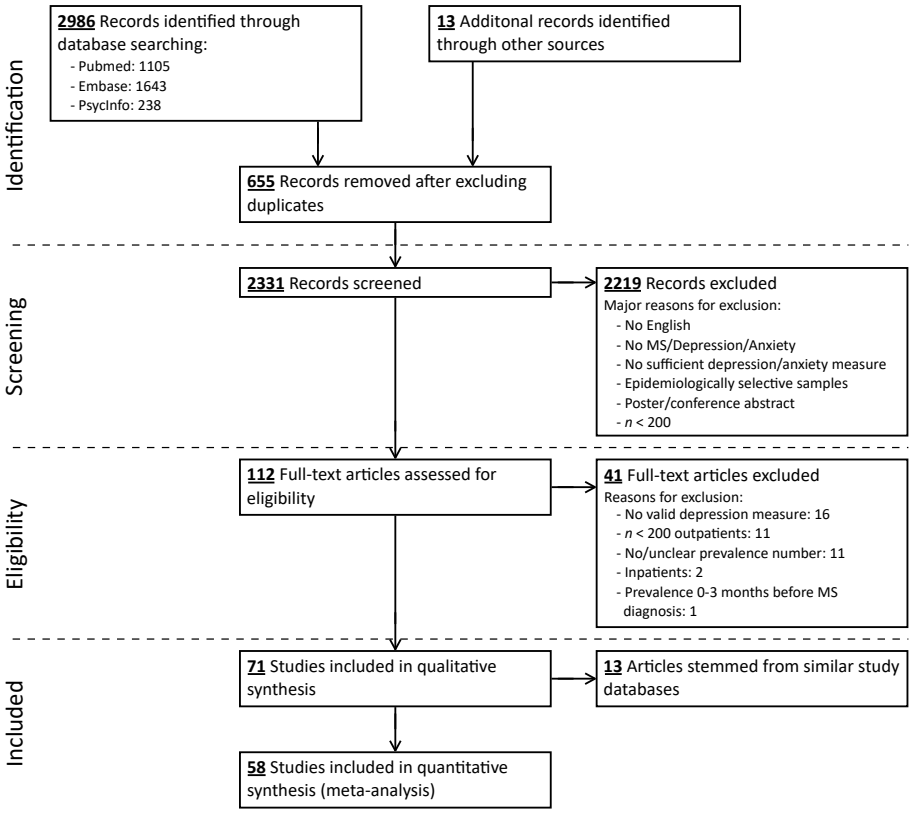

Figure 2.1 Flowchart of the extraction process.

supplementary material C and D, showing large variation in studied samples, assessment method, prevalence period, cut-off values and prevalence rates.

Depression

Prevalence rate

If depression was defined as a depressive disorder or a score above a defined cut-off on a depression rating scale, the weighed prevalence of all 58 studies on depression was 30.5% (95%CI=26.3%–35.1%). The I^2-statistic was 99.4%, meaning the heterogeneity was extremely high. An attempt was made to identify the intended subgroups.

Subgroup analysis: disorder versus symptoms

Sixteen studies reported prevalence rates of a depressive disorder identified with (semi) structured interviews, ICD or ICPC codes, and/or by a clinician. Forty-two studies used a cut-off on a depression rating scale to assess clinically significant depressive symptoms. Figure 2.2 shows that the pooled prevalence of a depressive disorder was 20.6% (95%CI=15.3%–27.1%) with a range from 1.3% to 44.1%. Prevalence of clinically significant depressive symptoms was higher compared with the prevalence of a depressive disorder showing a weighted mean of 35.0% (95%CI=30.1%–40.1%) and range from 9.3% to 76.2% (p=.001). High heterogeneity persisted. We conducted separate additional subgroup analyses for studies on depressive disorder and clinically significant symptoms. Results are displayed in Table 2.1 and Table 2.2.

Subgroup analysis: assessment method

Depressive disorder

Variety in assessment for a depressive disorder was large and heterogeneity remained high, independent of the subgroup we defined as shown in Table 2.1 Most diagnostic studies based their prevalence rate either on ICD-codes retrospectively retrieved from insurance databases or medical records, or on a semi-structured SCID interview. Five studies used (semi) structured interviews to establish DSM criteria. They displayed an average prevalence rate of 28.4% (95%CI=17.2%–43.2%) that at first glance seemed higher than the pooled prevalence of 11 studies using retrospective diagnosis by clinician or ICD/ICPC-codes, showing an average prevalence of 17.6% (95%CI=12.1%–24.9%). However, the subgroups did not significantly differ from each other.

Information on diagnostic measures and prevalence time was often lacking. In order to shed more light on the type of depressive disorder, a subgroup of six studies was defined, assessing current depressive disorder from 0 to 12 months, resulting in a weighted prevalence of 16.8% (95%CI=9.5%–27.9%). The average prevalence of the 10 studies that assessed life-time depressive disorder, depression in a specific time-period that lasted longer than 12 months or depressive disorder in medical records with undefined prevalence period, was 22.9% (95%CI=15.3%–33.0%). Of studies using (semi) structured interviews, two assessed current depressive disorder (20.4%, 95%CI=12.5%–31.6%) and three a depressive disorder over a year (34.9%, 95%CI=25.1%–46.3%), showing a borderline significant difference (p=.054).

Group by Disorder/Symptoms	Study name	Event rate	Lower limit	Upper limit
Disorder	Brenner *et al.* (2014)	0.044	0.040	0.048
Disorder	Buchanan *et al.* (2003)	0.360	0.352	0.368
Disorder	Carta *et al.* (2014)	0.264	0.207	0.329
Disorder	Demakis *et al.* (2009)	0.415	0.383	0.447
Disorder	Harel *et al.* (2007)	0.441	0.403	0.479
Disorder	Horton *et al.* (2010)	0.292	0.250	0.338
Disorder	Kang *et al.* (2010)	0.151	0.129	0.176
Disorder	Lo Fermo (2010)	0.013	0.007	0.025
Disorder	Marrie *et al.* (2013)	0.317	0.303	0.331
Disorder	Mohr *et al.* (2007)	0.258	0.208	0.314
Disorder	Nuyen *et al.* (2006	0.050	0.028	0.086
Disorder	Patten *et al.* (2003)	0.158	0.122	0.202
Disorder	Patten *et al.* (2005)	0.170	0.162	0.177
Disorder	Sadovnick *et al.* (1996)	0.344	0.284	0.409
Disorder	Simpson *et al.* (2014)	0.312	0.298	0.327
Disorder	Thielscher *et al.* (2013)	0.347	0.334	0.360
Disorder		**0.206**	**0.153**	**0.271**
Symptoms	Amtmann *et al.* (2014)	0.244	0.207	0.286
Symptoms	Asano *et al.* (2013)	0.170	0.137	0.209
Symptoms	Bamer *et al.* (2008)	0.477	0.449	0.505
Symptoms	Beal *et al.* (2007)	0.410	0.372	0.450
Symptoms	Coyle *et al.* (2014)	0.552	0.534	0.570
Symptoms	Da Silva *et al.* (2011)	0.304	0.256	0.358
Symptoms	Duquin *et al.* (2008)	0.436	0.381	0.494
Symptoms	Ensari *et al.* (2014)	0.387	0.330	0.446
Symptoms	Ferrando *et al.* (2007)	0.191	0.145	0.248
Symptoms	Hakim *et al.* (2000)	0.161	0.124	0.206
Symptoms	Hiele *et al.* (2012)	0.190	0.163	0.221
Symptoms	Holden *et al.* (2011)	0.440	0.378	0.504
Symptoms	Jensen *et al.* (2014)	0.264	0.230	0.301
Symptoms	Johansson *et al.* (2007)	0.422	0.357	0.491
Symptoms	Jones *et al.* (2012)	0.469	0.454	0.484
Symptoms	Kargarfard *et al.* (2012)	0.648	0.590	0.701
Symptoms	Kehler *et al.* (2009)	0.120	0.084	0.169
Symptoms	Koch *et al.* (2014)	0.293	0.269	0.317
Symptoms	Lobentanz *et al.* (2004)	0.561	0.513	0.608
Symptoms	Marrie *et al.* (2009)	0.650	0.640	0.659
Symptoms	Mattioli *et al.* (2011)	0.251	0.202	0.308
Symptoms	McGuigan *et al.* (2006)	0.284	0.228	0.349
Symptoms	Moreau *et al.* (2009)	0.255	0.205	0.312
Symptoms	Neau *et al.* (2012)	0.293	0.234	0.359
Symptoms	Patten *et al.* (2005)	0.328	0.291	0.368
Symptoms	Patten *et al.* (2010)	0.292	0.271	0.314
Symptoms	Patten *et al.* (2013)	0.294	0.274	0.315
Symptoms	Patti *et al.* (2007)	0.452	0.406	0.498
Symptoms	Patti *et al.*(2007)	0.262	0.228	0.299
Symptoms	Pittion-Vouyovitch *et al.* (2006)	0.738	0.679	0.790
Symptoms	Poder *et al.* (2008)	0.093	0.062	0.138
Symptoms	Porcel *et al.* (2006)	0.300	0.245	0.362
Symptoms	Pozilli *et al.* (2012)	0.537	0.486	0.588
Symptoms	Solari *et al.* (2004)	0.188	0.141	0.246
Symptoms	Sollom *et al.* (2007)	0.602	0.558	0.644
Symptoms	Somerset *et al.* (2001)	0.762	0.706	0.809
Symptoms	Spain *et al.* (2007)	0.160	0.133	0.192
Symptoms	Stepleman *et al.* (2014)	0.491	0.451	0.532
Symptoms	Verdier-Taillefer *et al.* (2001)	0.514	0.477	0.551
Symptoms	Viner *et al.* (2014)	0.260	0.228	0.296
Symptoms	Williams *et al.* (2005)	0.222	0.186	0.262
Symptoms	Zettl *et al.* (2013)	0.319	0.282	0.357
Symptoms		**0.350**	**0.301**	**0.401**

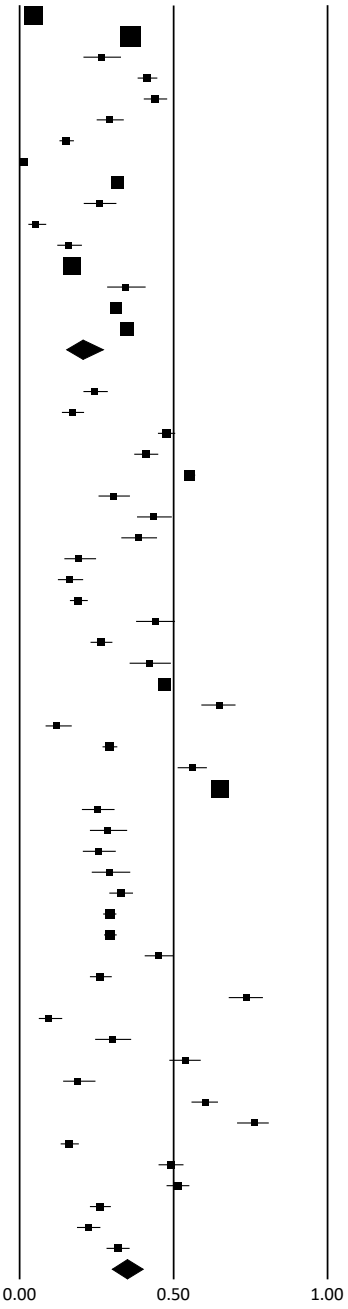

Figure 2.2 Forrest plot of the prevalence of depressive disorder and clinically significant depressive symptoms in MS patients. Larger markers indicate larger sample sizes.

Table 2.1 Subgroup analyses for studies on depressive disorder.

Subgroup analysis		No. of studies	Prevalence (%) *mean (95%CI)*	I^2 (%)	*p*-value
Assessment method	Retrospective code[1]	11	17.6 (12.1–24.9)	99.7	
	Diagnostic interview	5	28.4 (17.2–43.2)	95.3	
					.12
Prevalence period	Current (<13months)	6	16.8 (9.5–27.9)	99.5	
	>12 months	10	22.9 (15.3–33.0)	99.6	
					.35
	Current diagnostic interview	2	20.4 (12.5–31.6)	88.4	
	>12 months diagnostic interview	3	34.9 (25.1–46.3)	91.0	
					.054
Quality	Low/Moderate risk of bias	6	16.6 (9.9–26.4)	99.7	
	High risk of bias	10	23.3 (16.1–32.5)	99.2	
					.27
Patient source	Population-based	8	16.4 (10.4–24.9)	96.2	
	Not population-based	8	25.5 (16.8–36.7)	99.7	
					.14
	Outpatients	6	21.7 (13.2–33.5)	96.9	
	Nursing facilities	2	38.7 (18.7–63.3)	91.0	
	Insurance databases	5	14.6 (8.3–24.5)	99.6	
	General practice	3	20.0 (9.8–36.8)	97.1	
					.20
Region	USA/Canada	8	28.1 (18.3–40.5)	99.3	
	Europe	6	11.3 (6.3–19.6)	99.8	
	Rest: Middle East, Asia, Australia	2	27.3 (11.0–53.2)	99.3	
					.028*

* <.05; [1] retrospective diagnosis by clinician or ICD/ICPC-codes retrospectively retrieved from insurance databases or medical records.

Clinically significant depressive symptoms

Studies varied in measurements used to identify clinically significant depressive symptoms, and defined cut-off scores ranged from mild to severe depression. Studies mainly used the 'Center for Epidemiological Studies Depression Scale' (CES-D) [94], the 'Hospital Anxiety and Depression Scale' (HADS) [95], Beck Depression Inventory (BDI) [96], and 'Patient Health Questionnaire' (PHQ) [97] assessing depressive symptoms over the last week or two weeks. Subgroup analyses for different assessment scales showed the highest average prevalence rate for studies using the BDI-sf [98] (47.8%, 95%CI=29.6%–66.7%) and lowest for studies using the HADS (cut-off>10) (15.5%, 95%CI=7.7%–28.9%) with a trend towards statistical significance (p=.081). Table 2.2 shows that heterogeneity was considerable (I^2=91.3–99.6), but lower for studies performed with the PHQ-9

Table 2.2 Subgroup analyses for studies on clinically significant depressive symptoms.

Subgroup analysis		No. of studies	Prevalence (%) *mean (95%CI)*	I^2 (%)	*p*-value
Assessment method	HADS (cut-off >7)	5	28.4 (16.5–44.3)	91.3	
	HADS (cut-off > 10)	4	15.5 (7.7–28.9)	98.6	
	BDI SF (cut-off >3)	4	47.8 (29.6–66.7)	97.2	
	BDI (cut-off >10)	3	33.4 (16.9–55.2)	95.2	
	BDI-II (cut-off >19)	2	46.2 (22.1–72.2)	98.3	
	CES-D (cut-off >16)	7	37.5 (25.0–51.8)	99.6	
	PHQ-9 (cut-off >9)	4	23.9 (12.6–40.6)	41.8	
					.081
Quality	Low/Moderate risk of bias	23	32.4 (26.1–39.5)	99.2	
	High risk of bias	19	38.1 (30.5–46.3)	97.8	
					.29
Patient source	Population-based	18	36.2 (29.1–43.9)		
	Not population-based	24	34.1 (28.1–40.7)		
					.68
	Outpatients	22	33.8 (27.9–40.3)	96.7	
	MS society	12	35.1 (27.1–44.1)	99.3	
	General practice	2	53.0 (30.8–74.1)	99.0	
	≥25 MS clinics	2	25.9 (12.2–46.7)	0.00	
					.33
Region	USA/Canada	19	30.9 (24.2–38.7)	99.3	
	Europe	20	37.9 (30.3–46.0)	97.7	
	Rest: Middle East, Asia, Australia	3	42.5 (23.9–63.6)	99.1	
					.34

HADS = Hospital Anxiety and Depression Scale; BDI-SF = Beck Depression Inventory-Short Form; BDI = Beck Depression Inventory; BDI-II = Beck Depression Inventory, Second Edition; CES-D = Center for Epidemiological Studies Depression Scale; PHQ = Patient Health Questionnaire.

(I^2=41.8), demonstrating a pooled prevalence of 24%. Since clinically significant symptoms were assessed over the last week or two weeks, 'prevalence period' was not considered as a variable for subgroup analyses.

Subgroup analysis: quality of research paper

The quality was assessed for all studies according to the criteria shown in the supplementary material B. Half of the selected studies (*n*=29) was rated with a high risk of bias, 20 with moderate risk of bias and nine studies were rated with a low risk of bias. For 21 studies the target population

was a close representation of the national population, and most studies (*n*=52) used an acceptable case definition.

We defined good quality research papers as papers that were rated with low or moderate risk of bias. When all studies rated with a high risk of bias were excluded, the weighted prevalence for all studies on depression (n=29) was 28.5% (95%CI=22.8%–35.1%). Considering only studies with a low or moderate risk of bias, pooled prevalence for depressive disorder was 16.6% (95%CI=9.9%–26.4%), and 32.4% (95%CI=26.1–39.5) for clinically significant symptoms. For all analyses, heterogeneity remained high ($I^2 \geq 98$) and significant differences in prevalence estimates between high or moderate and low quality studies, were absent.

Subgroup analysis: patient recruitment resource

A distinction was made between studies performed in a clinical setting and population-based studies. Studies performed in a clinical setting comprised studies that assessed outpatients in clinical settings, used the national database of all residents in medicare- and mediair certified nursing facilities, or used health service data of Veterans. Population-based studies comprised studies that obtained population-based data from administrative health or insurance databases, health surveys, and (records of) general practitioner-practices. Also studies with patients recruited via MS societies and webpages, the web portal of the UK MS Register, MS support groups, and multicentre trials over 25 hospitals were classified in the population-based subgroup.

Studies on depressive disorder displayed a prevalence rate of 16.4% (95%CI=10.4%–24.9%) for population-based studies versus 25.5% (95%CI=16.8%–36.7%) for studies performed in the clinical setting *(p*=.14*)*. A significant difference for studies on clinically significant depressive symptoms performed in the population or in the clinical setting was also absent (36.2% versus 34.1%, respectively).

In addition, we defined smaller subgroups that existed of studies that assessed only outpatients, a subgroup with studies using the national database of medicare- and mediair certified nursing facilities, a subgroup with studies that used administrative health or insurance databases, one with studies with patients recruited via MS societies, a group with studies that collected data from general practitioner-practices, and a subgroup with multicentre trials over 25 hospitals. Heterogeneity remained high, and subgroups did not significantly differ. Prevalence of depressive disorders was 21.7% (95%CI=13.2%–33.5%) for outpatients, 38.7% (95%CI=18.7%–63.3%) for patients in nursing facilities, 14.6% (95%CI=8.3%–24.5%) in studies using insurance databases, and 20.0% (95%CI=9.8%–36.8%) for general practice research. Regarding clinical significant depressive symptoms, the weighted prevalence was 33.8% (95%CI=27.9%–40.3%) for outpatients, 35.1% (95%CI=27.1%–44.1%) when MS societies were the recruitment resource, 53% (95%CI=30.8%–74.1%) for two general practice studies, and 25.9% (95%CI=12.2%–46.7%) for two studies that recruited patients in multicentre trials.

Subgroup analysis: region

To compare findings between different regions, we defined subgroups for studies performed in North America, Europe, and Australia, Middle East and Asia together. Regarding depressive

disorder, these subgroups significantly differed *(p*=.028*);* European studies reported a lower prevalence (11.3%, 95%CI=6.3%–19.6%), compared with other regions (27.3% and 28.1%). For prevalence of clinically significant symptoms, there were no differences between regions with average prevalence rates ranging from 30.9% to 42.5%. Heterogeneity was >98% for all subgroups.

Anxiety

Prevalence rate

Studies on anxiety in MS (*n*=15) displayed a weighted prevalence of 22.1% (95%CI=15.2%–31.0%) when anxiety was defined as an anxiety disorder or a score above a defined cut-off on a self-report scale. Heterogeneity was extremely high (99.3%).

Subgroup analysis: disorder versus symptoms

Six studies described prevalence rate of an anxiety disorder and nine studies used a cut-off on a self-report scale to assess clinically significant symptoms of anxiety. Figure 2.3 shows that the pooled prevalence rate of an anxiety disorder was 9.8% (95%CI=5.1%–17.8%) and ranged from 1% to 35.6%. Pooled prevalence of studies that measured clinically significant symptoms of anxiety was significantly higher than the prevalence of an anxiety disorder showing a prevalence of 34.2% (95%CI=23.2%–47.1%) that ranged from 15.4% to 54.1 (*p*<.001). Heterogeneity remained higher than 98%.

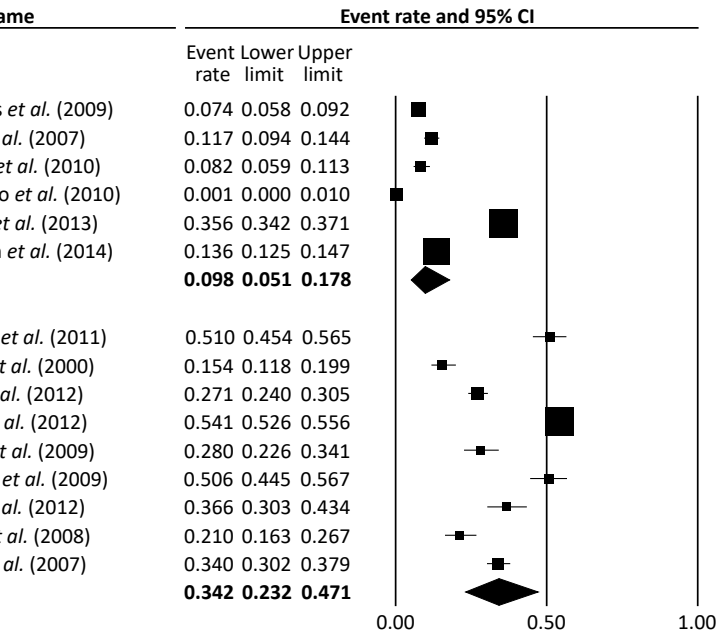

Figure 2.3 Forrest plot of the prevalence of anxiety disorder and clinically significant symptoms of anxiety in MS patients. Larger markers indicate larger sample sizes.

Subgroup analysis: assessment method

For additional subgroup analyses regarding studies on anxiety disorders and clinically significant symptoms, we were repeatedly faced with a small number of studies per subgroup and high heterogeneity (Table 2.3). Most studies on anxiety disorder used retrospective diagnosis in medical files with a weighted prevalence of 8.7% (95%CI=3.7%–19.0%). Assessed anxiety disorder present during a time period longer than a year was 13.2% (95%CI=4.4%–33.3%). Two studies assessed a current anxiety disorder (prevalence rate 2.7% (95%CI=0.4%–15.3%). To measure clinically significant symptoms of anxiety, the HADS [95] was most often used. Pooled prevalence rate was 46.2% (95%CI=33.5%–59.4%) for three studies using a cut-off >7 (I^2>98) and 24.5% (95%CI=16.7%–34.4%) for studies using a cut-off >10 (I^2=90.6), which was significantly different (p=.008).

Subgroup analysis: quality of research paper

For all 15 studies on anxiety, prevalence for good quality studies that were rated with a moderate or low risk of bias was 25.6% (95%CI=16.5%–37.6%), and 18.8% (95%CI=11.0%–30.2%) for with studies rated with a high risk of bias (p=.35). There was no difference in prevalence rate of an anxiety disorder assessed in good quality studies compared with low quality studies that were rated with a high risk of bias (17.4% versus 6.3%, p=.17). For studies on clinically significant symptoms of anxiety we observed a prevalence of 28.9% for good quality studies versus 46.0% for studies rated with high risk of bias which was not significant, p=.16). Heterogeneity remained high (I^2>93).

Subgroup analysis: patient recruitment resource

We divided studies in the same population and non-population-based subgroups as described previously for studies on depression. Analysis showed a weighted prevalence rate of 22.8% (95%CI=8.4%–48.7) for studies on anxiety disorder assessed in the population, which was significantly higher than the prevalence in non-population based samples 5.5% (95%CI=2.3%–12.5%, p=.031). No difference was found between studies on clinically significant symptoms in the population (33.7%) versus clinical samples (35.3%) or when we performed analyses for more specific subgroups with outpatients, or patients recruited from the MS society.

Subgroup analysis: regions

Whether studies were performed in Northern America, Europe or in other continents, did not make any difference for the prevalence of an anxiety disorder or clinically significant symptoms. Heterogeneity of studies on clinically significant symptoms in Europe was moderate (I^2>67) where all other subgroups analyses showed high heterogeneity.

Meta-regression analyses (post-hoc)

Although subgroup analyses were performed to assess sources of heterogeneity, large variation between studies was still present within each subgroup. By performing subgroup analyses, variables were investigated separately. Meta-regression analysis is an additional way of integrating

Table 2.3 Subgroup analyses for studies on anxiety disorder and clinically significant symptoms of anxiety.

		Anxiety disorder				Clinically significant anxiety symptoms			
Subgroup analysis		**No. of studies**	**Prevalence (%) *mean (95%CI)***	**I^2 (%)**	***p*-value**	**No. of studies**	**Prevalence (%) *mean (95%CI)***	**I^2 (%)**	***p*-value**
Assessment method	Retrospective code[1]	5	8.7 (3.7–19.0)	99.4					
Prevalence period	Current (<13months)	2	2.7 (0.4–15.3)	95.4					
	>12 months	4	13.2 (4.4–33.3)	99.3					
					.13				
	HADS (cut-off >7)					3	46.2 (33.5–59.4)	97.5	
	HADS (cut-off > 10)					4	24.5 (16.7–34.4)	90.6	
									.008**
Quality	Low/Moderate risk of bias	2	17.4 (5.5–43.6)	99.5		6	28.9 (18.3–42.4)	98.8	
	High risk of bias	4	6.3 (2.4–15.3)	90.5		3	46.0 (26.8–66.5)	83.4	
					.17				.16
Patient source	Population-based	2	22.8 (8.4–48.7)	99.8		6	33.7 (22.2–47.5)	98.6	
	Not population-based	4	5.5 (2.3–12.5)	88.8		3	35.3 (19.3–55.4)	95.9	
					.031*				.89
	Outpatients					3	35.3 (18.5–56.7)	95.9	
	MS society					5	30.6 (18.4–46.4)	98.9	
									.71
Region	USA/Canada	3	13.7 (3.2–42.7)	99.4		2	24.4 (11.2–45.3)	67.2	
	Europe	2	2.4 (0.3–16.7)	95.4		6	37.9 (26.2–51.1)	98.3	
	Rest: Middle East, Asia, Australia	-	-	-		-	-	-	
					.16				.25

* <.05; ** <.01; [1] retrospective diagnosis by clinician or ICD/ICPC-codes retrospectively retrieved from insurance databases or medical records; HADS = Hospital Anxiety and Depression Scale.

findings by combining multiple variables. We used version 3 of CMA to perform these post-hoc analyses. We found no indication for collinearity as the correlation between variables was lower than .55. We constructed a model for depressive disorders and for clinically relevant symptoms since they are different concepts resulting in different prevalence rates as was also shown by our subgroup analyses. For studies on depressive disorder the variables 'risk of bias', 'source', 'region', 'type of assessment', and 'prevalence time' were included in the regression model. For studies on depressive symptoms, 'risk of bias', 'source' and 'region' were added to the model. No meta-regression analyses were performed for studies on anxiety disorders and symptoms due to a small number of studies (<10). Results were in line with our subgroup analyses (supplementary mate-rial E).

DISCUSSION

Aim of this systematic review and meta-analysis was to estimate the prevalence of depression and anxiety in MS, and specifically to explore sources of heterogeneity by extensive analyses. This review elaborated on previous reviews on depression and anxiety in MS [1],[12],[14]. It included a large sample with more than 87,000 MS patients and investigated 23 studies that were not considered previously [14]. We demonstrated consistent evidence of high prevalence rates of depression (31%) and anxiety (22%) emphasizing the robustness of earlier findings. In line with the general depression literature [15], results from subgroup analyses stress the importance to differentiate between prevalence of clinically significant symptoms and disorders, as the prevalence of clinically significant depressive and anxiety symptoms in MS was elevated (35% and 34%) compared with disorders (21% and 10%). Prevalence of a depressive disorder was relatively lower in studies from Europe. For anxiety disorders we found different estimates according to recruitment resources with higher prevalence rates for community-based samples. However, despite our efforts to adequately enhance quality and decrease study differences, heterogeneity remained considerably high and subgroup- and meta-regression analyses did not reveal its sources.

The prevalence of a current depressive disorder (0-12 months, 17%) in our study is much higher compared with the general population where annual prevalence rates are around 6% (2%–10%) [99]–[101]. Also clinically significant depressive and anxiety symptoms, assessed over the last one or two weeks, seem elevated in MS compared with the general population [102],[103]. Our results approach prevalence estimates of reviews on depression or anxiety in other chronic medical illnesses as Parkinson's disease and diabetes. These reviews show prevalence rates of 17% [104], 13.6%, and 11% [105] for a depressive disorder, 14% for an (generalized) anxiety disorder [106], and highly elevated clinically significant symptoms of depression (35%, 31% [104],[105] and anxiety (40%) [106].

Although results are difficult to interpret due to high heterogeneity, the finding of relatively low prevalence of depressive disorders in European studies is not in line with the literature. A review on the WHO World Mental Health surveys using the CIDI to assess depressive or anxiety

disorder in the general population world-wide showed that these disorders are quite common in many countries throughout the world [107]. In our review, included studies were mainly conducted in Europe and North America. Studies with a sample size <200 were excluded to minimize selection bias. As a result well conducted studies with smaller sample sizes could have been eliminated as well as smaller studies from regions were the prevalence of MS is smaller such as Latin America. As a result, we cannot make worldwide conclusions on prevalence rates of depression and anxiety in MS, and more research with larger samples is needed. Further, we expected to find reduced mental comorbidity in patients recruited from community-based settings compared with clinical settings since percentages in the latter one are suggested to be more elevated [1],[17]. Our different findings could be related to the still large variation in study characteristics in the defined subgroups, and quality of papers on anxiety disorders as only two high-quality studies were included. An alternative explanation is that MS patients recruited from the community or clinical settings might not be so different from each other since MS concerns a relatively rare and complicated disease with most patients from the community consequently also visiting hospitals.

We were unable to explain the degree of heterogeneity. Explanations could be related to the variation of (untested) factors across studies underlining previous recommendations to develop a consistent approach to measure psychiatric comorbidity in MS [9],[14]. Although self-report scales can be useful for testing depression/anxiety in MS, their variation, appropriateness and different cut-off scores to assess clinically significant symptoms may have further contributed to high heterogeneity. Subgroup analyses showed prevalence of clinically significant anxiety symptoms assessed with the HADS to be higher when a low cut-off score (>7) was used compared with a more conservative cut-off (>10) which argues for consensus on a definitive cut-off point. Assessment methods often contained a number of questions related to physical symptoms of MS such as fatigue, sleep problems, and pain. Including these items could increase the score simply because a physical illness is present [1], which would plead for higher cut-offs. Evidence-based guidelines (2014) recommend the BDI self-report scale for assessing depression in MS patients [9]. Recent findings [108] support the idea that instruments to identify depression in patients without MS could be used to assess depression in MS, as the depressive symptom profile does not differ substantially between depressed patients with and without MS. Various self-report scales were recently validated against a clinical diagnoses of depression in MS patients and demonstrated good accuracy and provided appropriate cut-offs [94],[95],[97],[109]–[112]. In addition to the BDI, the PHQ and IDS-SR are widely used instruments. Both are freely available and translated in many languages, making them particular appropriate to screen and quantify depression in MS. Brevity of the PHQ is suggested to enhance feasibility of its use [109]. The IDS-SR offers a 16-item short version and can identify subtypes [113],[114] of depression in MS helping to elucidate biological substrates [110],[115].

Regarding assessment of depressive disorder, definitions often differ between hospitals, physicians, and prescription claims [65], and information on assessment method and prevalence period is frequently lacking, especially when data are extracted from medical records and community databases. The most widely used approach by psychiatrist to establish a depressive

disorder is the standardised interview which is based on the American Psychiatric Association's DSM-IV [19] and World Health Organization's ICD [20]. It is valid, uses rigorously defined criteria for depressive disorders, and forms the bulk of the clinical research on depressive disorders [15]. In our systematic review, only five included studies used (semi) structured interviews to establish DSM criteria, of which a mere two were rated with good quality. More studies with large population-based samples using diagnostic interviews are therefore encouraged [17]. However, these studies may require considerable effort and time. Although self-report scales cannot be used to make a formal diagnosis and tend to report higher rates compared with standard interviews, they can be used to quickly capture a range of depressive symptoms in MS, and as the first stage of a two-phase survey which also includes a diagnostic interview to determine actual cases of depressive disorder in MS [15],[116]. In addition, it was recently suggested to consider administrative databases with ICD codes to quantify depression in large population-based studies and worldwide potentially useful datasets were described [117].

Another clue for heterogeneity may be hidden in specific patient characteristics, which we were not able to analyze because of the lack of detailed information. Patients with similar MS durations could have very different disease courses, disability level, cerebral and spinal involvement, and (psychological) treatment, that each might influence mood or anxiety differently [1],[2]. There is evidence suggesting prevalence of depressive disorder to be higher among patients with progressive forms of MS compared with those with relapsing remitting MS (RRMS) [118]. On the contrary, other studies suggested that patients with primary progressive MS (PPMS) had lower life time risk of depressive disorder compared with RRMS patients [119], or found no association with disease course at all [11],[32]. To explore the relationship with disability level we post-hoc pooled depression prevalence of 10 studies who presented EDSS scores but high heterogeneity hampers conclusions on elevated depression rates in relation to MS severity (supplementary material F). As the majority of studies did not present data on psychological or pharmalogical (e.g. interferon-beta) treatment that may change mood, we could not take this information into account. This may have introduced bias and should be considered a limitation of our study. As differences in case mix between studies may cause unexplained variability, further analyses of these aspects may not only help to explain the observed heterogeneity and the elevated prevalence rates of depression and anxiety in MS, but also help clinicians to select MS patients who are at higher risk for depression and anxiety for more extensive examination since this may have therapeutic consequences. More extensive disease information of individual patients will be however required. Lack of access to individual patient data is a common limitation and researchers may consider proceeding to individual patient meta-analyses.

Limitations of the included studies may have further resulted in distorted findings in our review. The response rate of the majority of studies was often less than 68% suggesting a bias toward the more mobile and motivated patients [86]. Non-responders generally tend to report significantly more often depression or anxiety than respondents [120]. The majority of the included studies (95%) did not provide information on non-responders, limiting insight in the generalizability of the results. Population-based registries incorporated in standard MS care,

as is already applied in Scandinavia, will be most likely to present unbiased data and elevated response rate, leading to better estimates.

In conclusion, this systematic review confirms the increased prevalence of depression and anxiety in MS. It is also the first attempt to provide explanations for high heterogeneity observed. Sources of heterogeneity were not revealed by our extensive subgroup and meta-regression analyses which emphasizes the importance to agree on how to define depression and anxiety and how to recruit patients in order to improve prevalence estimates and to clarify their relation to specific patient characteristics.

Acknowledgements

This work was supported by the Stichting MS Research (Grant number 09-678).

We would like to express our thanks and acknowledge the help of Caroline Planting in the development of our search strategy.

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Supplementary Material 2.A Search Strategy.

Pubmed: ("Multiple Sclerosis"[Mesh] OR multiple sclerosis [tiab]) AND ("Depression"[Mesh] OR depression* [tiab] OR "Depressive Disorder"[Mesh] OR depressive*[tiab] OR "Anxiety"[Mesh] OR anxiet* [tiab] OR "Anxiety Disorders"[Mesh] OR anxious* [tiab] OR "Emotions"[Mesh] OR emotion* [tiab] OR "Affective Symptoms"[Mesh] OR affective symptom* [tiab] OR "Mood Disorders"[Mesh] OR mood disorder*[tiab] OR distress* [tiab] OR psychological* [tiab] OR mental [tiab] OR neurotic*[tiab]) AND (epidemiology[subheading] OR "Epidemiologic Studies"[Mesh] OR "Epidemiology"[Mesh:noexp] OR epidemiol*[tiab] OR "Prevalence"[Mesh] OR prevalence* [tiab])

Embase: ('multiple sclerosis'/exp OR 'multiple sclerosis':ab,ti) AND ('major affective disorder'/exp OR 'minor affective disorder'/exp OR 'mood disorder'/exp OR 'depression'/exp OR 'anxiety'/exp OR 'anxiety disorder'/exp OR 'emotion'/exp OR depression*:ab,ti OR depressive*:ab,ti OR 'major affective disorder':ab,ti OR 'minor affective disorder':ab,ti OR emotion*:ab,ti OR anxiet*:ab,ti OR anxious*:ab,ti OR mental:ab,ti OR 'mood disorder':ab,ti OR distress*:ab,ti OR psychological*:ab,ti OR neurotic*:ab,ti) AND ('epidemiology'/exp OR epidemiolog*:ab,ti OR 'prevalence'/exp OR prevalence*:ab,ti)

PsycInfo: (DE "Multiple sclerosis" OR TI multiple sclerosis OR AB multiple sclerosis) AND (DE "depression" OR TI depression* OR AB depression* OR DE "major depression" OR TI depressive* OR AB depressive* OR DE "affective disorders" OR TI affective disorders OR AB affective disorders OR TI mood OR AB mood OR DE "anxiety" OR DE "anxiety disorders" OR TI anxiety* OR AB anxiety* OR TI anxious* OR AB anxious* OR DE "emotions" OR TI emotion* OR AB emotion* OR DE "distress" OR TI distress OR AB distress OR DE "psychological stress" OR TI psychological stress OR AB psychological stress*.OR TI psychological* OR AB psychological* OR TI mental OR AB mental) AND (DE "epidemiology" OR TI epidemiolog* OR AB epidemiolog* OR TI prevalence* OR AB prevalence*)

Supplementary Material 2.B Risk of Study Bias.

Authors	1	2	3	4	5	6	7	8	9	10	11
Amtmann *et al.* (2014)	High	Low	Low	High	Low	Low	Low	Low	Low	Low	Mod
Asano *et al.* (2013)	High	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Bamer *et al.* (2008)	Low	High	High	High	Low	Low	Low	Low	Low	Low	Mod
Beal *et al.* (2007)	High	Low	High	Low	Low	Low	Low	Low	Low	Low	High
Brenner *et al.* (2014)	Low	High	Low	Low	Low	Low	Low	Low	Low	Low	Mod
Buhanan *et al.* (2003)	High	Low	Low	Low	Low	Low	Low	Low	Low	Low	High
Carta *et al.* (2014)	High	Low	Low	High	Low	Low	Low	Low	High	Low	High
Coyle *et al*. (2014)	High	Low	High	High	Low	Low	Low	Low	Low	Low	High
Da Silva *et al.* (2011)	High	High	Low	High	Low	Low	Low	Low	Low	Low	High
Demakis *et al.* (2009)	Low	Low	Low	High	Low	Low	High	Low	High	Low	Mod
Duquin *et al.* (2008)	High	High	High	High	Low	Low	Low	Low	Low	Low	High
Ensari *et al.* (2014)	Low	High	High	Low	Low	Low	Low	Low	Low	Low	High
Ferrando *et al.* (2007)	High	Low	Low	Low	Low	Low	Low	Low	Low	Low	Mod
Hakim *et al.* (2000)	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Harel *et al.* (2007)	High	High	Low	Low	Low	Low	Low	High	Low	Low	High
Hiele *et al.* (2012)	Low	Low	Low	Low	Low	Low	High	Low	Low	Low	Mod
Holden *et al.* (2011)	High	Low	High	Low	Low	Low	Low	Low	Low	Low	Mod
Horton *et al.* (2010)	High	Low	Low	High	Low	High	High	Low	High	Low	High
Jensen *et al.* (2014)	High	Low	High	Low	Low	Low	Low	Low	Low	Low	Mod
Johansson *et al.* (2007)	High	Low	Low	Low	Low	Low	Low	Low	Low	Low	Mod
Jones *et al.* (2012)	High	Low	Low	High	Low	Low	Low	Low	Low	Low	Low
Kang *et al.* (2010)	Low	Low	High	Low	High	Low	High	Low	Low	Low	High
Kargarfard *et al.* (2012)	High	Low	Low	Low	Low	Low	Low	Low	Low	Low	Mod
Kehler *et al.* (2009)	Low	High	High	Low	High	High	High	High	High	High	Mod
Koch *et al.* (2014)	High	High	High	High	Low	Low	Low	Low	Low	Low	High
Lobentanz *et al.* (2004)	High	High	High	High	Low	Low	Low	Low	Low	High	High
Lo Fermo *et al.* (2010)	High	High	Low	Low	Low	Low	Low	High	Low	High	High
Marrie *et al.* (2013)	Low	Low	Low	Low	Low	Low	Low	Low	High	Low	Low
Marrie *et al.* (2009)	Low	Low	Low	High	Low	Low	Low	Low	Low	Low	Low
Mattioli *et al.* (2011)	High	High	Low	High	High	Low	Low	Low	Low	Low	High
McGuigan *et al.* (2006)	High	High	High	Low	Low	Low	Low	Low	Low	Low	Mod
Mohr *et al.* (2007)	High	Low	Low	High	Low	Low	Low	Low	Low	Low	Mod
Moreau *et al.* (2009)	High	Low	High	High	Low	Low	Low	Low	Low	Low	High
Neau *et al.* (2012)	High	High	High	High	Low	Low	Low	Low	Low	Low	High
Nuyen *et al.* (2006)	Low	High	Low	Low	Low	High	High	High	High	Low	Mod
Patten *et al.* (2013)	Low	Low	Low	High	Low	Low	Low	Low	Low	Low	Low
Patten *et al.* (2010)	High	Low	Low	High	Low	Low	Low	Low	Low	Low	Mod
Patten *et al.* (2005)	High	Low	High	Low	Low	Low	Low	Low	Low	Low	Mod

Authors	1	2	3	4	5	6	7	8	9	10	11
Patten *et al.* (2005)	Low	Low	Low	Low	High	High	High	High	High	Low	High
Patten *et al.* (2003)	Low	High	Low	High	Low	Low	Low	Low	Low	Low	Mod
Patti *et al.* (2007)	High	Low	Low	Low	Low	Low	Low	Low	Low	Low	High
Patti *et al.* (2007)	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Pittion Vouyovitch *et al.* (2006)	High	High	High	Low	Low	Low	Low	Low	Low	Low	High
Poder *et al.* (2008)	High	High	Low	Low	Low	Low	Low	Low	Low	Low	Mod
Porcel *et al.* (2006)	High	Low	Low	Low	Low	Low	Low	Low	Low	Low	High
Pozilli *et al.* (2012)	High	Low	High	High	Low	Low	Low	Low	Low	Low	Mod
Sadovnick *et al.* (1996)	High	High	High	Low	Low	Low	Low	Low	High	Low	High
Simpson *et al.* (2014)	Low	Low	Low	Low	Low	High	High	Low	Low	Low	High
Spain *et al.* (2007)	Low	High	Low	High	Low	Low	Low	Low	Low	Low	Mod
Solari *et al.* (2004)	High	High	High	High	Low	Low	Low	Low	Low	Low	High
Sollom *et al.* (2007)	Low	High	High	Low	Low	Low	Low	Low	Low	Low	High
Somerset *et al.* (2001)	Low	Low	Low	High	Low	Low	Low	Low	Low	Low	Low
Steppleman *et al.* (2014)	High	High	High	High	Low	Low	Low	Low	Low	Low	High
Thielscher *et al.* (2013)	Low	High	Low	Low	Low	Low	Low	Low	High	Low	High
Viner *et al.* (2014)	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Verdier-Taillefer *et al.* (2001)	High	High	High	High	Low	Low	Low	Low	Low	Low	High
Williams *et al.* (2005)	High	High	Low	High	Low	Low	Low	Low	Low	Low	High
Zettle *et al.* (2013)	High	High	High	High	Low	Low	Low	Low	Low	Low	High

External Validity:

1. Was the study's target population **a close representation** of the national population in relation to relevant variables, e.g. age, sex, occupation?
2. Was de the sampling frame a **true or close representation** of the target population?
3. Was some form **of random selection** used to select the sample, OR was a census undertaken?
4. Was the likelihood **of non-response bias** minimal?

Internal Validity:

5. Were data collected **directly form the subjects**
6. Was an acceptable case definition used in the study?
7. Was the instrument that measured the parameter of interest (e.g. prevalence of low back pain) shown to have **reliability and validity** (if necessary)?
8. Was the **same mode of data collection** used for all subjects?
9. Was the **length of the shortest prevalence period** for the parameter of interest appropriate?
10. Were **numerator(s) and denominator(s)** for the parameter of interest appropriate?

Summary item on the overall risk of study bias:

11. - **Low risk of bias:** Further research is very unlikely to change our confidence in the estimate.
    - **Moderate risk of bias:** Further research is likely to have an important impact on our confidence in the estimate and may change the estimate.
    - **High risk of bias:** Further research is very likely to have an important impact on our confidence in the estimate and is likely to change the estimate.

Supplementary Material 2.C Characteristics of the study designs.

	Authors (publication year)	Country	Study (population) / Selection method	Number of analyzed patients	Age (mean, SD)	Gender, Female
1.	Amtmann *et al.* (2014)	USA, Washington	Part of a longitudinal study to examine/ compare psychometric properties of PHQ-9, CESD-10, PROMIS. Recruitment of convenience random subset sample through mailing list from national MS society.	455	52.9 (10.8)	82.9%
2.	Asano *et al.* (2013)	Canada Quebec	Cross-sectional survey of a randomly selected eligible sub- sample from 2 MS clinics.	417	43 (10)	77%
3.	Bamer *et al.* (2008)	USA East/ West Washington	Cross-sectional epidemiologic study of a large community sample. An email survey was sent to all eligible members of the MS association of King country and National MS Society.	1239 East(e): 520 West(w): 719	e:52.4 (11.2) w: 49.2 (11.3)	e: 75% w: 78%
4.	Beal *et al.* (2007)	USA Texas	Convenience sample of a longitudinal study of quality of life in chronic illness.	607	50.6 (10.28)	83%
5.	Brenner *et al.* (2014)	Sweden	Population-based prospective cohort: Longitudinal integration database for health insurance and labor market studies (LISA).	10750	47 (11)	70%
6.	Buchanan *et al.* (2003)	USA	Analyses of admission data of residents in all medicare-medicaid-certified nursing homes.	14009	57.5 (13.9)	70.3%
7.	Carta *et al.* (2014)	Italy	Case-control study with consecutive MS outpatients of one MS centre.	201	38.9 (10.04)	69.7%
8.	Coyle *et al.* (2014)	USA	Prospective open-label study for MS patients who receive immune modulatory therapy from 3 specialty pharmacies.	2966	49 (10.3)	80.4%
9.	Da Silva *et al.* (2011)	Northern Portugal	Case-control study with consecutive patients from one hospital.	312	39.5 (10.8)	65.7 (*n*=205)
10.	Demakis *et al.* (2009)	USA	Nursing home residents with MS: nationals database of all residents in medicare- and mediair certified nursing facilities.	924	55.82 (13.0) (*n*=269) 57.46 (12.9) (*n*=365)	10.8%

Response rate	Inclusion criteria	Moment of assessment	MS diagnose	Depression / Anxiety measure (cut-off)	Risk of bias L/M/H
21%	Missing	2008 Fifth time point	Self-report	PHQ-9 (>9) (also PROMIS, CES-D 10 (>9)	M
80%	-Definite MS/CIS -19-65 year -French/English -Lived in community -EDSS<7 -Not cognitive impaired	Missing	Diagnosis possible/definite MS or CIS at 2 MS clinics	HADS-d (>7)	L
e: 50.8% w: 39.3%	Missing	1999-2003	Self-report and physician confirmed diagnosis by MRI, lumbar puncture/evoked potentials	CES-D (>15) 16-20: mild 21-25: moderate >25: severe	M
>85%	Missing	1999	Self-report	CES-D10 (>9)	H
NA	-17-65 year -Living in Sweden in 2005 -No missing data	2000-2005	Being hospitalized or receiving specialized care at least once between 2000-20005 with primary/ secondary diagnosis ICD-10, code G35	Depressive disorder: ICD 10 (F32, F33). (Depression between 2000-2005) (>12 months)	M
NA	-All residents regardless of payment source	1998-2000	Via MS clinic	ICD-9-CM (code: 311) (at admission)	H
Missing	Missing	2011-2013	Diagnosis according Mc Donald criteria	ANTAS-SCID (>12 months)	H
22%	-≥18 years -MS diagnosis -Immuno- modulatory therapy	Missing	-Reported diagnosis by MRI (80%) -Treatment by neurologist (75%)	PHQ-9 (≥ 3 points on first 2 questions)	H
Missing	-MS exacerbation >1 month -No CNS disorder, dementia or serious comorbidity	Missing	Definite MS according Mc Donald revised criteria	HADS (>7 and >10)	H
NA	Missing	2000-2003	ICD-9 340	Depression/ Anxiety: diagnosis coded by physician 4 year prevalence	M

	Authors	Country	Study (population) / Selection method	Nr. of analyzed patients	Age (mean, SD)	Gender, Female
11.	Duquin *et al.* (2008)	USA	Study on validity of the entire MACFIMS battery in a sample prospectively accrued MS patients. Patients entered the study for participation in brain imaging research, routine monitoring of cognitive function or referral for evaluation of a specified management problem related to suspected cognitive impairment.	291 Research volunteer (RV): 77 Routine monitoring group (RM): 106, Clinically complex group (CC) :128	45.4 (8.9) RV: 42.4 (8.5) RM: 46.8 (9.3) CC: 45.6 (8.6)	Missing
12.	Ensari *et al.* (2014)	USA	Longitudinal study over 2.5 years. Recruitment through advertisement posted on MS society website and distributed through 12 Midwestern chapters.	269	45.9 (9.6)	82.9%
13.	Ferrando *et al.* (2007)	USA New York	Consecutive patients in MS clinic.	225	43 (12)	68
14.	Hakim *et al.* (2000)	Southern England	Population based survey of MS patients in county of Hampshire in Southern England. Patients were identified from hospital records and records of general practitioners and MS society.	305	48.3 (19-82)	Ratio 1:2.1
15.	Harel *et al.* (2007)	Israel (Tel Hashomer)	Retrospective analyses of computerized database. Consecutive patients were recruited at time of outpatient visits at the MS centre.	651	43.6 (12.5)	73%
16.	Hiele *et al.* (2012)	The Netherlands	Community-based sample. Recruitment through MS foundation, advertisement, meetings, MS nurses and neurologist.	715	48.3 (10.4)	74%
17.	Holden *et al.* (2011)	UK, Sheffield	Case-control study. Patients were recruited via internet forums of MS Society and University.	234	43.3 (9.7)	84%
18.	Horton *et al.* (2010)	USA, Canada	Validation study. Out-patients were recruited from 2 MS clinics.	404	46.5 (11.8)	76%
19.	Jensen *et al.* (2014)	USA, Washington	Part of longitudinal survey study of persons with physical disabilities in the University of Washington. Postal survey study with convenience sample that participated in previous survey studies, some recruited through print and web advertisements.	584	54.5 (10.8)	82%

Response rate	Inclusion criteria	Moment of assessment	MS diagnose	Depression / Anxiety measure (cut-off)	Risk of bias
Missing	-No Relapse/ corticosteroid treatment <4 weeks -No psychiatric disorder other than mood, personality, behavioral change, drug/alcohol dependence/abuse -No medical disorder other than MS affecting cognition	2006	Diagnosis by neurologist according Mc Donald criteria	BDI-FS (>3)	H
NA	-RRMS -Relapse free>30 days, ambulatory with/without assistance	2008-2009	Confirmed in writing treating physician	HADS (>7)	H
91%	Missing	Missing	Missing	PHQ-9 (≥10)	M
74%	Missing	1986-1989	Poser criteria confirmed by medical registrar visiting patients at home	HADS (>10) Depression Anxiety	L
NA	Missing	1997-2003	Diagnostic Poser criteria MS (in Database MS center)	SCID (DSM-III) depressive, anxiety disorders (Part of baseline and follow-up assessments of all MS patients)	H
75%	-≥18 year	2008	Self-report MS	HADS (no cut-off given)	M
NA	-18-65 years -Access to internet	Missing	Self-report Diagnosis from a consultant neurologist	CMDI-9 (>23)	M
Missing	-MS or CIS (*n*=10) -No severe cognitive impairment or impaired visual/upper extremity function	2008-2009	Self-report/ medical record	Diagnosis in Medical record (Prevalence period not known)	H
91%	->18 years -One time been outpatient in MS clinic	2009-2013	No confirmation of diagnosis, diagnosis was condition for entering registry	PHQ (>9)	M

	Authors	Country	Study (population) / Selection method	Nr. of analyzed patients	Age (mean, SD)	Gender, Female
20.	Johansson *et al.* (2007)	Sweden, Stockholm	Cross-sectional study carried out at MS centre. Patients were eligible outpatients with an appointment with one of the two senior neurologists.	206	47 (12) (n=219)	68% (n=219)
21.	Jones *et al.* (2012)	UK	Observational study using MS Web portal of UK MS Register that functions as a questionnaire delivery platform at registration. Adults with MS living in the UK could enrol in web portal of the UK MS Register that provides information on their experiences of living with MS, since May 2011.	4290 (depr) 4287 (anx)	50.9 (11.5) (*n*=4617)	71% (*n*=4617)
22.	Kang *et al.* (2010)	Taiwan	Population-based controlled study with a National health insurance research dataset covering >98% of the population of patients who sought ambulatory care/ hospitalization.	898	Missing	Missing
23.	Kargarfard *et al.* (2012)	Iran	Cross-sectional study with consecutive patients referred to MS society/clinic.	281	36.3 (7.4)	63.4% (*n*=178)
24.	Kehler *et al.* (2009)	Canada	MS patients recruited through advertisements on MS society website, posters and clinics across Canada (self-selected internet sample).	233	41.82 (10.19) (*n*=246)	81.6% (*n*=200)
25.	Koch *et al.* (2014)	Canada	MS clinic in Southern part province of Alberta.	1376	45.6 (10.8)	77%
26.	Lobentanz *et al.* (2004)	Austria	All members of the Vienna chapter of Austrian MS Society were sent postal questionnaires.	504 (417 responders)	50.6 (±13.1) (19.6-88.5) *n*=504	71.8% (*n*=504)
27.	Lo Fermo *et al.* (2010)	Italy	Retrospective study of medical records of patients with MS. Symptoms at onset MS in files collected.	682	Missing	Missing

Response rate	Inclusion criteria	Moment of assessment	MS diagnose	Depression / Anxiety measure (cut-off)	Risk of bias
85%	Missing	2002	Diagnosis according Poser criteria (interview), medical file	BDI (>9) & BDI-18	M
NA	-Adults	2011	Self-report MS	HADS (>7)	L
NA	->15 year -2 consensus MS diagnoses	2006-2007	Two consensus MS-diagnoses during 2007	Depressive disorders: ICD-9 (296.2, 296.3, 300.4, 301.12, 309,311) Comorbidities occurred either in an inpatient setting or as ≥ 2 ambulatory care claims in 2006/2007 (annual prevalence)	H
86%	-Diagnose of MS	2009	Missing	BDI-II (>19) 20-28:moderate ≥29: severe	M
NA	-≥18 years -MS -Living in Canada	Missing	Reporting a confirmed diagnosis	HADS (>10) Depression Anxiety	M
Missing	Missing	2002-2010	Clinical database info & Disease course evaluated by MS neurologist within six months	CES-D (>15)	H
53%	Missing	Missing	Missing	ZDS (≥50) 51-59: mild 60-69: moderate ≥70: severe	H
NA	Missing	1997-2007	Defined MS diagnosis	Psychiatric disorder with clinical characteristics of a depressive, anxiety episode in medical records. Symptoms at onset MS in files collected by using chart review anchored to the criteria of DSM-IV at onset MS	H

	Authors	Country	Study (population) / Selection method	Nr. of analyzed patients	Age (mean, SD)	Gender, Female
28.	Marrie *et al.* (2013)	Canada Manitoba	Population-based matched cohort from administrative health data which provides health care services for more than 98% of Manitoba residents for the 1 to 5 years periods ending in fiscal year 2005/06.	4192	Missing	Missing
29.	Marrie *et al.* (2009)	USA	Cross-sectional study using self-report registry for patients with MS (North American Research Committee On MS). Patients enrolled via web page, direct mailings and MS support groups.	8983	52.7 (10.4)	75.8%
30.	Mattioli *et al.* (2011)	Italy	Consecutive MS patients at MS centre of Brescia.	255	40 (11.3)	62%
31.	McGuigan *et al.* (2006)	Ireland	Epidemiological study on two Irish counties. Patients were referred by GP's in Wexford and Donegal counties, neurologists and MS society throughout Ireland.	211	46.5 (range= 19-78)	72%
32.	Mohr *et al.* (2007)	USA, California	Cross-sectional study. Patients treated by 35 neurologists were recruited through the Kaiser Permanente Medical Care group using an 'opt in' strategy over a period of 12 months.	260	51 (10.5)	73%
33.	Moreau *et al.* (2009)	France	Prospective multicenter study conducted in 65 centers.	255	37.8 (9.9)	76%
34.	Neau *et al.* (2012)	France	Prospective survey with randomly selected consecutive MS-outpatients. Patients were recruited in outpatient waiting rooms of private/public neurologists.	205	43.7 (11.1)	76%
35.	Nuyen *et al.* (2006)	The Netherlands	Cross-sectional study using morbidity data collected by 134 GP's in 75 general practices concerning an unselected cohort of patients with depression, stroke, MS, Parkinson's disease, dementia, migraine and epilepsy.	241 (of 276921)	49.1 (12.7)	69.7%
36.	Patten *et al.* (2013)	Canada	Prospective data in MS clinic that is a population-based service covering the Southern part of the province Alberta. All patients were emailed.	1876	46.2 (11.3) *n*=2053	76.4 (*n*=2053)

Response rate	Inclusion criteria	Moment of assessment	MS diagnose	Depression / Anxiety measure (cut-off)	Risk of bias
NA	-18 years of older ->2 separate physician claims, hospitalisation or perception claim (1984-2007) or >1 claim for persons resident in 2004	1984-2006	Medical file	Depressive /Anxiety disorders: ICD-9/10 296.2, 296.3, 300.4, 301.12, 309, 311	L
55.7%	-MS Symptom onset >15 and <60 years	2006	Self-report, validated in a randomly selected sample	CES-D (>15 and >20)	L
Missing	Missing	2008	Polman criteria	BDI-SF (>3)	H
58%	-History of clinically definite or probable MS by Poster criteria -No history of depression -No antidepressants	Missing	Poser criteria	BDI-II (>19) <19: minimal/ mild >19: moderate/ severe	M
52%	-Diagnosis of MS in database confirmed by neurologist	Missing	Diagnosis in Medical database, confirmed by neurologist/ patient	MDD DSM-IV (Tel. SCID) (Point prevalence)	M
Missing	-18-75 year -RRMS -Disease onset <5 years -No relapse <30 days -Starting Interferon Beta treatment	2002-2004	Missing	BDI (≥8) 4-7: mild 8-15: moderate ≥16: severe Stai-state:≥38 Stai-trait:≥40	H
Missing	-No Cognitive impairment -EDSS<8 - >1month Oral / intravenous methylprednison treatment	Missing	By neurologist	HADS (>10)	H
NA	Missing	Part of Dutch national survey of GP (2001)	ICPC code: N86 MS	ICPC-codes of life time depression (P76) and anxiety (P74, 79) -Diagnoses during contacts within 1-year period -Diagnoses on a 'problem list' of relevant (past) health problems	M
Missing	Missing	2002-2006	Self-report	CES-D (>15)	L

	Authors	Country	Study (population) / Selection method	Nr. of analyzed patients	Age (mean, SD)	Gender, Female
37.	Patten *et al.* (2010)	Canada	Prospective data from the Canadian Impact of MS database. Registered patients are from MS clinic and were emailed to complete follow-up ratings.	1670	18-34 (15.9%) 35-44 (29.5%) 45-54 (33.6%) ≥55 (21%)	77.1% (*n*=1324)
38.	Patten *et al.* (2005)	Canada, Calgary, Southern Alberta	Cross-sectional baseline data collected from subjects in a prospective cohort study at a population-based MS clinic. Study questionnaire was emailed.	567	48 (range 19-76)	75.7%
39.	Patten *et al.* (2005)	Canada, Alberta	Retrospective study from population database from universal public insurance system.	8999	Missing	Missing
40.	Patten *et al.* (2003)	Canada	Data from a large scale population-based Canadian Community Health survey.	322 (of *n*= 115071)	Missing	Missing
41.	Patti *et al.* (2007)	Italy	Multicentre study with consecutive outpatients from 40 Italian MS centers.	587	<40 year: *n*=404	70.7%
42.	Patti *et al.* (2007)	Italy Catania, Florence, Bari, Genova	Cross-sectional multicentre study (6 centres). 100 consecutive outpatients at each MS centre were enrolled	445	43 (12.1)	71.5%
43.	Pittion-Vouyovitch *et al.* (2006)	France	Outpatients in hospital in Nancy were selected as part of European database of EDMUS.	237	42.5 (10.9)	71%
44.	Poder *et al.* (2008)	Canada Halifax, Nova Scotia	Cross-sectional study in a consecutive clinic-attending sample of MS patients.	236 (Depr) 233 (Anx)	46.1 (10.6) *n*=245	82% *n*=245

Response rate	Inclusion criteria	Moment of assessment	MS diagnose	Depression / Anxiety measure (cut-off)	Risk of bias
Missing	Missing	2002-2006	Self-report (whether a diagnosis of depression was made by a medical doctor)	CES-D (>15)	M
92%	Missing	Missing	Missing/ Neurologist-rated MS functional status scores were available from clinical files of 350 subjects	CES-D (>15)	M
NA	->14 years in 2000	1985-2002	Physician ICD billing codes	Affective disorder: 6 ICD-9 codes: 269.x: major affective disorder, 298: depressive psychosis, 300.4: Dysthemia, 309: adjustment disorder, 311: depressive disorder NOS. (Annual prevalence)	H
Missing	-≥18 years	2000-2001	Self-report	Major Depressive Disorder DSM-IV CIDI-sf ≥5 symptoms) (Annual prevalence)	M
91%	-Clinically definite diagnosis of MS -EDSS 1 - 5.5 -RRMS -Stable disease on enrolment -≥18years -No progressive course -No liver/renal disease or concomitant diseases	2000-2001	Missing	BDI (≥11) (mild to severe)	H
90%	->1 year MS (RR, PP, SP) ->18 year	2002-2003	By neurologist	BDI (>10) 11-17: mild 18-23: moderate 24-39: severe	L
76%	-Clinically definite MS -EDSS<6.5 -No other chronic disease	Missing	Definite MS based on Poser criteria	BDI-SF (>3) 4-7: mild 8-15: moderate >15: severe	H
91%	-No enrolment in trials -No cognitive impairment (EDSS mental≥2)	2006	Medical file, McDonald criteria	HADS (>10)	M

	Authors	Country	Study (population) / Selection method	Nr. of analyzed patients	Age (mean, SD)	Gender, Female
45.	Porcel *et al.* (2006)	Spain	MS patients who started IFN$_{\beta}$ treatment in at least the previous four years in one MS clinic.	233	Missing	70.3% (*n*=226)
46.	Pozilli *et al.* (2012)	15 countries (Germany, France, Czech republic, the Netherlands, Spain, Portugal, Middle East, Saudi Arabia, Turkey, Asia)	Prospective observational cohort on supportive strategies to improve adherence to IFN beta-1b (Beta plus study). Patients were recruited at neurological practices/ specialised neurological centres.	363 out of 1077 Middle East: 59.2% Europe: 39,8 Far East: 0.9%	35.9 (10.2)	71% (*n*=764)
47.	Sadovnick *et al.* (1996)	Canada, Vancouver	Cross-sectional study. Consecutive MS patients, both new referrals and seen for routine follow-up at MS clinic.	221	Missing	71.5%
48.	Simpson *et al.* (2014)	Scotland	Case-control study: Large nationally representative primary care population dataset. Holds clinical information of one third of Scottish population, by 314 general practitioners. Data is extracted in 2007 and is a complete copy of all historical data at that point.	3826	53.4 (12.8)	72.3%
49.	Spain *et al.* (2007)	Australia Victoria	Cross-sectional study. Patients were recruited through MS society, public and private neurology clinics.	580	46.7 (*n*=687)	79% (*n*=687)
50.	Solari *et al.* (2003)	Italy	Case-control study in MS outpatients concerning validation of the CMDI: Chicago Multiscale Depression Inventory.	213	38 (9.2)	66%
51.	Sollom *et al.* 2007	UK	Three-phase postal survey study as part of another study. Participants were recruited via articles in magazine of MS society inviting anyone with MS to participate in a study about MS and mood.	495	45.8	81%
52.	Somerset *et al.* (2001)	UK: Scotland and England	Cross-sectional survey in stratified sample with MS. 67 randomly selected GP-practices out of 200 approached, agreed to participate and forwarded questionnaires to MS patients.	260	<45:28% 45-54: 32% 5-64: 22% >64: 17%	70%

Response rate	Inclusion criteria	Moment of assessment	MS diagnose	Depression / Anxiety measure (cut-off)	Risk of bias
89%	Missing	1995-1999	Missing	BDI (>10) 10-15: mild >15: mild to moderate	H
Missing	-Switched to IFNB-1b in 1-3 months -RR/SP	Missing	Physician	CES-D (Europe: 16 <55 year, ≥55= 20 Middle east: 21 Asia: 19)	M
97%	-No EDDS>6.5, MS-relapse, substance abuse, participation in trials	1992-1993	ICD-9-cm (code 340)	SCID (DSM-III) Current or life time	H
NA	-≥25 years	2007	Read code for MS using code-set by NHS Scotland information Services Division.	Clinician recorded Depression Read OR 4 antidepressants prescriptions <12 months. Anxiety Read code OR 4 anxiolytic/ hypnotic prescriptions/ 10/25 mg amitriptyline (<12 months)	H
Missing	Missing	Missing	Diagnosis confirmed by neurologist according Poser's criteria and cerebral MRI	HADS (>7)	M
Missing	-No history of alcohol/drug abuses -18-60 year -No central nervous system disease other than MS -No exacerbation/ steroid treatment<3 months	Missing	By neurologist	CMDI-moodscale: 23 (cut-off 1.5 SD above mean controlgroup)	H
NA	≤65 year	Missing	Self-reported type of MS	CES-D (>16)	H
68% (non-responders analyses)	Missing	Missing	Registered with MS in general practices	BDI-SF (no cut-off)	L

	Authors	Country	Study (population) / Selection method	Nr. of analyzed patients	Age (mean, SD)	Gender, Female
53.	Stepleman *et al.* (2014)	Southeastern USA	Five years of archival (medical records) data from MS center.	576	45.6 (11.42) (*n*=283)	82% (*n*=283)
54.	Thielscher *et al.* (2013)	Germany	Retrospective study based on data from IMS disease analyser database that collates from GP and specialists computer systems of 1109 GPs in 882 General practices.	5137	45.2 (13.2)	70.9%
55.	Viner *et al.* (2013)	Canada, 10 provinces	Cross-sectional survey of patients living with neurological conditions in Canada (SLNCC) (linked with National Canadian Community health survey that uses a probability sample of 70000 subjects and inquiries about medical conditions).	630	51.8	73.3%
56.	Verdier-Taillefer *et al.* (2001)	France	Study to verify validation of CES-D in a community-based sample including MS volunteers. A questionnaire was mailed to about 2000 of the volunteers.	696	47.0 (7.2)	63.2%
57.	Williams *et al.* (2005)	USA (Washington, Idaho, Alaska, Oregon)	Cohort study linking computerized medical records with a mailed self-report survey. Eligible veterans who received Veteran Health Administration services between 1995-2000 were emailed a survey.	451	55.1	13.6%
58.	Zettl *et al.* (2013)	Germany	Multicenter prospective observational non-interventional cohort study in the care of hospital neurological departments and office practices.	593	38.3 (10.3) (*n*=700)	70.9% (*n*=700)

L = Low; M = Moderate; H = High; SD = Standard Deviation; MS = Multiple Sclerosis; PHQ-9 = Patient Health Questionnaire; CESD = Center for Epidemiological Studies Depression Scale; PROMIS = Patient Reported Outcomes Measurement Information System; USA = United states of America; CIS = Clinical Isolated Syndrome; HADS = Hospital Anxiety and Depression Scale; MRI = Magnetic Resonance Imaging; EDSS = Expanded Disability Status Scale; RR = Relapsing Remitting; NA = Not Applicable; ICD = International Classification of Disease; ANTAS SCID = Advanced Neuropsychiatric Tool and Assessment Schedule Structured clinical interview for DSM Disorders; DSM = Diagnostic and Statistical Manual of psychiatric disorders; MACFIMS = Minimal Assessment of Cognitive Function in Multiple Sclerosis; BDI-SF = Beck Depression Inventory - Short form; CMDI = Chicago Multistate Depression Inventory; MDD = Major Depressive Disorder; ZDS = Zung's Self Rating Depression Scale; Depr = Depression; Anx = Anxiety; GP = General Practitioner; ICPC = International Classification of Primary Care; IFNB = Interferon Beta; NHS Scotland = National Health; UK = United Kingdom.

Response rate	Inclusion criteria	Moment of assessment	MS diagnose	Depression / Anxiety measure (cut-off)	Risk of bias
Missing	Missing	2003	Medical chart information	BDI-FS (>3)	H
missing	-MS between 2002-2007 -No MS/ depression before index rate -No cancer -Seen physician once yearly -2<index date>5	2000-2012	ICD-code G35	ICD-10 (F32, F33=MDD single/recurrent) First diagnoses of depression ≤5 after index date	H
82%	->15 years	2011-2012	Self-report on 18 neurological conditions	PHQ (>9)	L
65%	-30-60 years	Missing	Self-report	CES-D (>16 men) (>22 women)	H
43.7%	-ICD-9 MS diagnosis/ medication	Missing	ICD-9 MS diagnosis/ medication	PHQ-9 Major depr: (≥5), Minor depr: (≥3) symptoms more days than not, one either depressed mood/ anhedonia)	H
Missing	->18 years -CIS or RRMS -IFN beta-1b <3 months	2009-2011	Missing	CES-D (>15)	H

Supplementary Material 2.D Prevalence of depression and anxiety and additional information on Multiple Sclerosis.

	Authors	n	Type MS	EDSS: (mean, SD) / %
1.	Amtmann *et al.* (2014)	455	RR: 56.7% Other types: 41.3% Missing: 9%	51% EDSS: moderate level
2.	Asano *et al.* (2013)	417	RR: 263 (82%) P: 45 (14%)	Median: Men: 2.5 (IQR1.5-4.0) Women: 2 (IQR 1-3.5)
3.	Bamer *et al.* (2008)	1239 East (e) 520, West (w) 719	West: RR: 52% SP: 30% PP: 18% East: RR: 55% SP: 35% PP: 10%	West 1-4: West: 23% East: 35% 4.5-6: West: 48% East: 41% 6.5-9.5: West: 30% East: 24%
4.	Beal *et al.* (2007)	607	RR: 40% PP: 18% SP: 17% Benign: 10%	Missing
5.	Brenner *et al.* (2014)	10750	Missing	Missing
6.	Buchanan *et al.* (2003)	14009	Missing	Missing
7.	Carta *et al.* 2014)	201	Missing	Missing
8.	Coyle *et al.* (2014)	2966	RR: 2136 SP: 351 PP: 437 PR: 26 CIS: 8	3.2 Median: 3.5 (IQR 0-5.5)
9.	Da Silva *et al.* (2011)	312	RR: 80.4% SP: 9,9% PP: 9.6%	2.8 (2.2)
10.	Demakis *et al.* (2009)	924	Missing	Missing
11.	Duquin *et al.* (2008)	291	RR: 69% SP: 27% PP: 2%	RV: 2.7 (1.9) RM: 3.2 (1.8) CC: 3.1 (1.8)
12.	Ensari *et al.* (2014)	269	RR: 100%	Missing

MS onset in years (mean, SD)	MS / Depression treatment	Results (Prevalence)
14.4 (10.0)	Missing	Depression severity: 24.4% (CES-D10: 37.1%)
8 (3)	Missing	Depression severity: 17.0% (Women: 13%, Men: 4%)
West: 12.5 (9.5) East: 15.0 (10.2)	(East: *n*=542) 41%: Antidepressants Prozac: *n*=52 Celexa: *n*=29 Elavil: *n*=27	Depression severity: 47.7% Total sample e&w: (>20: 31.8%) 16-20: w15%, e18% 20-25: w12%, e10% 26-60: w19%, e24%
13.3 (7.4)	Missing	Depression severity: 41.0%
Missing	35% Psychiatric medication 25% Antidepressants	Depressive disorder: 4.4%
Missing	Missing	Depressive disorder: 36.0%
9.8 (9.4) (age: 28.4)	Missing	Depressive disorder: 26.4% (>12 months prevalence)
9.5	GA: 1475 IFNB 1a im: 604 IFNB 1a sc: 470 IFNB 1b: 417	Depression severity: 55.2%
9.32 (7.78)	40.4%: Interferon-B 7.7%: Anxiolytic 12.8%: Antidepressant 13.8%: Anxiolytic and Antidepressant	Depression severity ≥8= 30.4% ≥11=10.6% Anxiety severity ≥8= 51% ≥11= 26.6%
Missing	Medications (across study)= 31.45 (15.49)	Depressive disorder: 41.5% Anxiety disorder: 7.4%
Missing	Missing	Depression severity: 43.6% RV: 35.1% RM: 47.2% CC: 44.5%
8.8 (7)	Modifying therapy: *n*=223	Depression severity: 38.7%

	Authors	n	Type MS	EDSS: (mean, SD) / %
13.	Ferrando *et al.* (2007)	225	Missing	Missing
14.	Hakim *et al.* (2000)	305	Missing	Missing
15.	Harel *et al.* (2007)	651	Missing	Missing
16.	Hiele *et al.* (2012)	715	RR: 35% SP: 17% PP: 9% Unclear: 28%	Missing
17.	Holden *et al.* (2011)	234	RR: 71% SP: 12% PP: 9% Unknown: 8%	
18.	Horton *et al.* (2010)	404	CIS: 2.5% RR: 70.7% SP: 16.1% PP: 7.7% Unknown: 3%	Missing
19.	Jensen *et al.* (2014)	584	Missing	Missing
20.	Johansson *et al.* (2007)	206	RR: 58% SP: 38% PP: 4%	0: 0.5% 1-3.5: 59% 4-5.5: 17% 6-9.5: 23.5%
21.	Jones *et al.* (2012)	4290(depr) 4287(anx)	RR: 61.7% PP: 14.4% SP: 9.4% Non known: 14.5% (*n*=4540)	Missing
22.	Kang *et al.* (2010)	898	Missing	Missing
23.	Kargarfard *et al.* (2012)	281	RR: 64.1% PP: 10.3% SP: 25.6%	3.39 (1.79)
24.	Kehler *et al.* (2009)	233 (depression 232 anxiety	RR: 65% PP: 14% SP: 14% Benign: 1.6% (*n*=231)	Missing

MS onset in years (mean, SD)	MS / Depression treatment	Results (Prevalence)
Missing	Missing	Depression severity: 19.1%
15.8	Missing	Depression severity: 16.1% Anxiety severity: 15.4%
11.5 (9.2)	Missing	Depressive disorder: 44.1% Anxiety disorder: 11.7%
10.8 (6.8) (*n*=14 missing)	Missing	Depression severity: 19.0% Anxiety severity: 27.1%
4.56 (2.5)	64%: Disease modifying prescription medication 45%: Antidepressants	Depression severity: 44.0%
13.9 (10.1)	Missing	Depressive disorder: 29.2% Anxiety disorder: 8.2%
Missing	Missing	Depression severity: 26.4%
14 (10)	Missing	Depression severity: 42.2% BDI: Mild: 29.5% BDI: Moderate: 10.5% BDI: Severe: 2% BDI-18: Mild: 21.5% BDI-18: Moderate: 7% BDI-18: Severe: 0.5%
12.2 (9.4) (*n*=2265)	Missing	Depression severity: 46.9% (Women: 32%, Men: 15%) Anxiety severity: 54.1% (Men=14%, Women=40%)
Missing	Missing	Depressive disorder: 15.1%
9.38 (5.73)	Missing	Depression severity: 64.8% Mild: 35% Moderate: 32% Severe: 32%
87.12 (10.19) months (*n*=246)	Missing	Depression severity: 12.0% Anxiety severity: 28.0%

	Authors	n	Type MS	EDSS: (mean, SD) / %
25.	Koch *et al.* (2014)	1376	RR: 64% SP: 18% PP: 10% Unknown: 8%	3.4 (2.2)
26.	Lobentanz *et al.* (2004)	504 (417 responders)	Missing	5.77 (+-1.9) n=2 missing
27.	Lo Fermo *et al.* (2010)	682	Missing	Missing
28.	Marrie *et al.* (2013)	4192	Missing	Missing
29.	Marrie *et al.* (2009)	8983	Missing / RR: 98.1% P: 10.9% (*n*=5458)	Missing
30.	Mattioli *et al.* (2011)	255	RR: 88% Chronic Progressive:12%	2.37 (1.2): Non-depressed: 3.35 (2.33): Depressed
31.	McGuigan *et al.* (2006)	211	RR: 52.1% SP: 28.9% PP: 19%	4.3 (0-9): moderate/ severe depression 4.5 (0-9): minimal/ mild depression
32.	Mohr *et al.* (2007)	260	Missing	Missing
33.	Moreau *et al.* (2009)	255	RR: 100%	1.4 (1.2)
34.	Neau *et al.* (2012)	205	RR: 63.4% SP: 29.2% PP: 7.4%	3.0 (2.3) (range 0-7)
35.	Nuyen *et al.* (2006)	241	Missing	Missing
36.	Patten *et al.* (2013)	1876		<6: 70.6% ≥6: 32.9%
37.	Patten *et al.* (2010)	1670	Missing	5.1

MS onset in years (mean, SD)	MS / Depression treatment	Results (Prevalence)
12.2 (9.6)	Anti-depressants: 24%	Depression severity: 29.3%
15.8 +-11.3	Missing	Depression severity: 56.1% mild: 20.6% moderate:16.3% Severe: 9.3%
Missing	Missing	Depressive disorder: 1.3% Anxiety disorder: 0.1%
Missing	Only described for validation cohort (*n*=430)	Depressive disorder: 31.7% Anxiety disorder: 35.6% (>12 months prevalence)
Missing/ 22.9 (11.1) (*n*=5458)	80.8%: Treatment for mental-comorbidity with life time MDD + CES-D>20 (*n*=1884)	Depression severity: >15: 65.0% >20: 31.2%
8.52 (6.27): Non-depressed 9.45 (5.98): Depressed	B-Interfrons: *n*=108 Glatiramer acetate: *n*=32 Natalizumab: *n*=27 Fingolimod: *n*=15 Mitoxantrone: *n*=1	Depression severity: 25.1%
14.6 (1-44)	Missing (Antidepressant is exclusion criteria)	Depression severity: 28.4% Moderate/Severe: 28% Minimal/Mild: 43%
Missing	Antidepressant: 23% of the 26% with Major Depressive Disorder	Depressive Disorder: 25.8%
5.1 (15.7)	Interferon Beta	Depression severity: 25.5% Severe: 6.3% Moderate: 19.2% Mild: 20.4% Anxiety severity: 50.6%
139 (99.9) months (8-504)	53%: Immune modulatory agents 24.8%: Symptomatic depression treatment	Depression severity: 29.3% Anxiety severity: 36.6%
Missing	Missing	Depressive disorder: 5.0% Anxiety disorder: 1.2%
Missing	Missing	Depression severity: 29.4%
33	Missing	Depression severity: 29.2%

	Authors	n	Type MS	EDSS: (mean, SD) / %
38.	Patten *et al.* (2005)	567	RR: 30.77% SP: 22.4% PP: 9.5% PR: 8.7% Unknown: 28.7%	Missing
39.	Patten *et al.* (2005)	8999	Missing	Missing
40.	Patten *et al.* (2003)	322	Missing	Missing
41.	Patti *et al.* (2007)	587	RR: 100%	0-2: *n*=417
42.	Patti *et al.* (2007)	445	RR: 59% SP: 29% PP: 12%	Median: 4.0 (2.3)
43.	Pittion-Vouyovitch *et al.* (2006)	237	RR: *n*=147 SP: *n*=70 PP: *n*=20	3.7 (1.7)
44.	Poder *et al.* (2008)	236 (dep) 233 (anx)	RR: 70% SP: 23% PP: 7%	Missing
45.	Porcel *et al.* (2006)	233	RR: 82% SP: 18%	2 (0-8.5) *n*=182 3 (1-7) *n*=52
46.	Pozilli *et al.* (2012)	363	RR:74% SP: 26%	3.3 (1.9)
47.	Sadovnick *et al.* (1996)	221	Missing	Missing
48.	Simpson *et al.* (2014)	3826	Missing	Missing
49.	Spain *et al.* (2007)	580	RR: 54% SP: 30% Indeterminate:6%	Median: 3.5
50.	Solari *et al.* (2004)	213	RR: 78% SP: 18% PP: 4%	2.9

MS onset in years (mean, SD)	MS / Depression treatment	Results (Prevalence)
Missing	8.5%: Disease modifying therapy Glatiramer acetate: *n*=22 Interferon beta: *n*=28	Depression severity: 32.8%
Missing	Missing	Depressive disorder: 17.0%
Missing	Missing	Depressive disorder: 15.7%
0-2: *n*=337 3-5: *n*=127 5-10: *n*=66 ≥10: *n*=55	Not previously treated with disease-modifying agents or immunosuppressant	Depression severity: 26.2%
13.6 (9.3)	MS Therapy: 29.4%: None 53.9%: Interferon 7%: Interferon and other DMAs 9.7%: Other DMAs	Depression severity: 45.2% 11-17: 28.1% 18-23: 15% 24-39: 2.1%
9.8 (7.4)	Missing	Depression severity: 73.8% Mild: 19.4% Moderate: 39.2% Severe: 15.2%
14.4 (9.2)	Missing	Depression severity: 9.3% Anxiety severity: 21%
		Depression severity: 30.0% 10-15: 20.6% >15: 9.4%
89.6 (74.6) (months)	Missing	Depression severity: 53.7%
Missing	Missing	Depressive disorder: 34.4%
Missing	Missing	Depressive disorder: 31.2% Anxiety disorder: 13.6% (< 12 months prevalence)
8.53 (7.5)	Missing	Depression severity: 16.0% Anxiety severity: 34.0%
9.1 (6.9)	Interferons: 42% Immunosuppressants: 12% Glatiramer: 4% Antidepressants: 8% Anxiolytics: 6% Muscle relaxants: 7%	Depression severity: 18.8%

	Authors	n	Type MS	EDSS: (mean, SD) / %
51.	Sollom *et al.* (2007)	495	RR: 45% Chronic progressive: 32.5% (10% PP) Unknown: 18%	Missing
52.	Somerset *et al.* (2001)	260	Benign: 16% RR: 33% RP: 15% P: 36%	Missing
53.	Stepleman *et al.* (2014)	576	Missing	Missing
54.	Thielscher *et al.* (2013)	5137	Missing	Missing
55.	Viner *et al.* (2014)	630	Missing	Missing
56.	Verdier-Taillefer *et al.* (2001)	696	Missing	Missing
57.	Williams *et al.* (2005)	451	Progressive subtype: 59.4%	Missing
58.	Zettl *et al.* (2013)	593	RR: 94.6% CIS: 5%	2 (1.4)

SD = Standard Deviation; MS = Multiple Sclerosis; EDSS = Expanded Disability Status Scale; RR = Relapsing Remitting; SP = Secondary Progressive; PP = Primary Progressive; P = Progressive; Depr = Depression; Anx = Anxiety; DMA = Disease Modifying Agents; MDD = Major Depressive Disorder; CESD = Center for Epidemiological Studies Depression Scale; IFNB = Interferon Beta; RV = Research Volunteer; RM = Routine Monitoring group; CC = Clinically Complex group; CIS = Clinical Isolated Syndrome.

MS onset in years (mean, SD)	MS / Depression treatment	Results (Prevalence)
Missing	37.2%: taking antidepressants (>16 CES-D, *n*=298)	Depression severity: 60.2%
Missing	Missing	Depression severity: 76.2% Mild: 28% Moderate: 33% Severe: 15%
6.99 (6.88)	Added psychotropic meds: 17% Increased psychotropic meds: 9% Decreased psychotropic meds: 4% Psychological consult: 27% Referral psychiatrist: 4% Referral psychologist: 2% (n=279)	Depression severity: 49.1%
Missing	Antidepressants: 67%	Depressive disorder: 34.7% (Women: 37.2%, Men: 28.5%)
Missing	Missing	Depression severity: 26.0%
Missing	Missing	Depression severity: 51.4%
18.1 (12.5)	35.3%: Disease modifying therapy	Depression severity: 22.2% Minor depressive symptoms: 32%
Missing	Interferon beta-1b: 100%	Depression severity: 31.9%

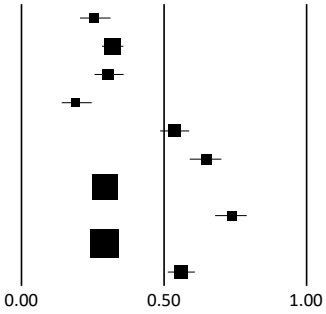
Supplementary material 2.E Meta-regression analyses (post-hoc) for studies on depressive disorder and clinically significant depressive symptoms.

	Disorder (*n*=16)			Symptoms (*n*=42)		
Covariate	**Coeffi-cient**	**Standard error**	**2-sided *p*-value**	**Coeffi-cient**	**Standard error**	**2-sided *p*-value**
Quality						
High versus Moderate/Low risk of bias	-0.83	0.64	0.20	-0.29	0.25	0.24
Patient source						
Not population versus Population-based	0.24	0.65	0.71	0.12	0.25	0.63
Region						
Europe versus Rest (Middle East, Asia, Australia)	0.44	0.94	0.64	0.40	0.48	0.41
Europe versus USA/Canada	1.38	0.63	0.029*	-0.21	0.25	0.40
Assessment method						
Retrospective code[1] versus Diagnostic interview	0.57	0.65	0.38			
Prevalence period						
Current (<13months) versus >12 months	0.77	0.60	0.20			

* p<.05; [1] retrospective diagnosis by clinician or ICD/ICPC-codes retrospectively retrieved from insurance databases or medical records.

Supplementary material 2.F Prevalence of depression for different EDSS score. Larger markers indicate larger sample sizes.

Study name	Subgroup within study	Event rate	Lower limit	Upper limit
Moreau *et al.* (2009)	(mean = 1.4)	0.255	0.205	0.312
Zettl *et al.* (2013)	(mean = 2.0)	0.319	0.282	0.357
Da Silva *et al.* (2011)	(mean = 2.8)	0.304	0.256	0.358
Solari *et al.* (2004)	(mean = 2.9)	0.188	0.141	0.246
Pozilli *et al.* (2012)	(mean = 3.3)	0.537	0.486	0.588
Kargafard (2011)	(mean = 3.4)	0.648	0.590	0.701
Koch *et al.* (2014)	(mean = 3.4)	0.293	0.269	0.317
Pittion-Vouyovitch *et al.* (2006)	(mean = 3.7)	0.738	0.679	0.790
Patten *et al.* (2010)	(mean = 5.1)	0.292	0.271	0.314
Lobentanz *et al.* (2004)	(mean = 5.8)	0.561	0.513	0.608



3

MAJOR DEPRESSIVE DISORDER IN MULTIPLE SCLEROSIS: DIFFERENT OR SIMILAR?

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ABSTRACT

Background: Major depressive disorder (MDD) is common in patients with Multiple Sclerosis (MS) but may remain unrecognized because of overlapping symptoms and different presentation due to its specific MS-related neurobiological aetiology. We aimed to investigate the clinical profile of MDD in MS.

Methods: In a sample of MDD patients with MS (*n*=83) and without MS (*n*=782), MDD characteristics, 30 depressive symptoms, and sum scores of cognitive, somatic, atypical and melancholic symptom clusters were compared using logistic regression analyses and analysis of co-variance.

Results: MDD in MS was characterized by older age of onset ($p<.001$), and fewer comorbid anxiety disorders (37% versus 72%, $p<.001$). The symptom 'future pessimism' was more common in MS patients (OR=1.62, 95%CI=1.02–2.59). 'Diminished capacity for pleasure/enjoyment' (OR=0.44, 95%CI=0.24–0.78), 'increased appetite' (OR=0.40, 95%CI=0.19–0.85), 'arousal symptoms' (OR=0.49, 95%CI=0.28–0.84) and 'panic/phobic symptoms' (OR=0.49, 95%CI=0.29–0.84) were less common in MS patients. Twenty-five symptoms (83%) out of 30, including depression's core symptoms (sadness and loss of interest) were not differentially associated with MS and no differences existed for the symptom clusters.

Conclusions: Only subtle differences in depression symptomatology existed between MDD patients with and without MS. The clinical profile of depression remains valid among MS patients, although diminished anxiety distress and comorbidity suggest a purer form of MDD.

INTRODUCTION

Major depressive disorder (MDD) is common in Multiple Sclerosis (MS) and its prevalence is substantially higher compared with the general population [1],[2]. Although depression has enormous impact on the quality of life of MS patients, it is often not adequately diagnosed and treated [3]–[5]. This might be partly due to overlapping psychiatric and neurological symptoms such as fatigue, psychomotor slowing, and sleeping problems. Recognizing depression and selecting appropriate treatment could therefore be a major improvement for MS patients and their clinicians [3],[4].

The underlying neurobiology of MS may play an important role in the increased prevalence and expression of depression in MS patients. Structural brain changes, elevated Hypothalamic-Pituitary-Adrenal (HPA)-axis activity and immune-inflammatory dysregulations are related to presence and severity of depression in MS. Abnormalities in both the limbic and endocrine system may be more closely related to affective and cognitive depressive symptoms in MS [6],[7], whereas MS-inflammatory markers showed stronger correlations with neurovegetative symptoms [6],[8]. Inflammatory dysregulations and elevated HPA-axis activity also play a significant role in atypical and melancholic subtypes of MDD [9]. One might therefore expect more atypical and melancholic features in depressed MS patients due to shared pathophysiological pathways.

Research concerning the clinical profile of MS-related MDD is still scarce. One study found depressed and non-depressed MS patients to be best differentiated by symptoms of 'sadness', 'pessimism', 'sense of failure', 'guilt', 'disappointment', and 'changes in appetite and/or weight' [10], whereas another recent study showed depressive symptoms measured with the Beck Depression Inventory-II to be similar in moderate or severe depressed MS patients compared with MDD patients without MS [11]. So, earlier conclusions have been inconsistent, and were generally based on small samples and self-reported depression. Examination of the depressive symptom profile in a larger representative MS sample with a clinical diagnosis of MDD is therefore a subsequent step to substantiate whether the concept of depression is similar in patients with and without MS.

This study aims to compare 30 depressive symptoms and four symptom clusters (cognitive, somatic, atypical, melancholic) in a sample with moderate or severe MDD, including patients with or without MS, taking into account clinical characteristics. Furthermore, the presence of comorbid anxiety disorder(s) will be addressed since MDD and anxiety disorders often co-occur. Research on comorbid MDD and anxiety disorders in MS received little attention yet which is unfortunate since co-occurrence of depression and anxiety in the general population has been associated with worse clinical outcomes than in MDD alone [12]. By combining a well-defined MS sample and a large cohort with clinical MDD diagnoses, this study makes a significant contribution to the understanding of the clinical phenotype of MS-related depression.

METHODS

Study sample

Data were derived from i) a randomized controlled trial (RCT) investigating the effectiveness of internet-based cognitive behaviour therapy for depressed MS patients [13], and ii) an ongoing multi-center cohort study 'the Netherlands Study of Depression and Anxiety' (NESDA) examining the long term course and consequences of depression and anxiety disorders in patients with current or remitted depressive and/or anxiety disorders as well as healthy controls [14]. Both study protocols were approved centrally by the Ethical committee of the VU University Medical Center, and for NESDA subsequently by the review boards of the University Medical Center Groningen and Leiden University Medical Center. All patients provided written informed consent.

MS patients (*n*=178) participating in the RCT were recruited at several MS centres throughout the Netherlands, and through calls in MS newsletters and Internet-sites. The methods have been described previously [13]. Participating patients were 18 years or older with sufficient command of Dutch language, and were not receiving psychotherapy or taking antidepressant medication less than 6 weeks. Psychiatric comorbidity other than MDD was no reason for exclusion. Baseline assessment took place between August 2011 and September 2015. Patients completed the self-report Inventory of Depressive Symptomatology (IDS-SR) [15] in addition to other baseline assessments.

The NESDA sample consisted of 2,981 adults aged 18 to 65 years who were recruited from the general population, primary health care, and specialised mental health care facilities in the Netherlands, and completed baseline assessment between September 2004 and February 2007. Exclusion criteria were insufficient command of Dutch language, and a primary clinical diagnosis of an obsessive compulsive disorder, bipolar disorder or severe addiction disorder. Psychiatric treatment was allowed. A detailed description of the NESDA study design and sampling procedures can be found elsewhere [14].

From both study bases, we included the following participants for the present study: those with a) a current (i.e. past 6 months) MDD diagnosis according to DSM-IV criteria assessed with the Composite International Diagnostic Interview (CIDI, World Health Organization version 2.1 [16]), and b) a score ≥26 on the self-report IDS-SR indicating moderate to (very) severe depressive symptoms [15],[17]. By excluding patients with no or mild depressive symptoms, sufficient depression severity and amount of variation were warranted in order to enhance comparison of symptom profiles. This selection resulted in a sample of 865 patients (782 from NESDA, 83 from the RCT). MS patients were only included from the RCT sample as all 6 patients from the NESDA sample with MS did not have a MDD diagnosis.

Assessment

MS and patient characteristics

MS diagnosis was based on self-report and a confirmed diagnosis by the neurologist of each patient. Self-report data on sociodemographic characteristics including age, sex, and education level were collected. Also self-report antidepressant use was assessed since this can introduce

bias in interpreting the clinical depression profile. Different types of antidepressants could have different effects on depressive symptoms and its side effects could change the MDD profile by influencing specific symptoms as weight gain or constipation [18]. Patients were classified as antidepressant users if antidepressant medication was taken 6 weeks or longer. For patients from the NESDA study, besides self-report, antidepressant use was also obtained by drug container inspection of all drugs used in the past month and classified according to the World Health Organization Anatomical Therapeutic Chemical classification [19].

In the MS sample, MS-specific questions were self-reported medication use, MS duration and course (confirmed by the neurologist). The telephone version of the Expanded Disability Status Scale [20] was used to assess the physical disability level. Although findings on the relation between depression and MS-related factors such as disease course, duration and physical disability are inconsistent [4],[21], disease-related factors could be of importance for a better understanding of MS-related depression. We therefore investigated the relation between disease-related factors (course, duration, disability level, medication) and depression severity in the MS-sample additionally.

Depression characteristics and depressive symptoms

Age of depression onset, information on the current episode (recurrence) and presence of a co-morbid dysthymic and/or anxiety disorder in the past six months were assessed with the CIDI [16] by trained research staff. Anxiety disorders involved panic disorder with or without agoraphobia, social phobia, generalized anxiety disorder and agoraphobia.

Depression severity was assessed with the 30-item IDS-SR [15], a self-report instrument that assesses all DSM-IV criteria for MDD, plus commonly associated symptoms (e.g. anxiety, irritability) and symptoms relevant to melancholic and atypical features over the past week. Each item has four answering options from 0 (no problems) to 3 (severe problems). The total severity score of the IDS-SR is calculated as the sum score of all items with a higher score indicating a higher severity. The IDS-SR showed good psychometric properties and was recently validated for MS patients [17],[22].

To determine the presence of individual depressive symptoms, IDS-SR items were recoded into dichotomous variables; a score of 0 or 1 means the symptom is absent, a score of 2 or 3 indicates its presence [23]. The separate items on appetite increase and decrease were recoded into a single three category variable: no change (score of 0 or 1 on both variables), decreased appetite (score of 2 or 3 on appetite loss), or increased appetite (score of 2 or 3 on appetite gain). Weight gain and weight loss were recoded similarly. Finally, the item on diurnal variation was recoded into a dichotomous symptom to distinguish patients with a worse mood in the morning from patients with no worse mood in the morning or no diurnal variation, as MDD is especially characterized by a worse mood in the morning.

To assess more homogeneous depressive symptom clusters, individual dichotomized symptoms of the IDS-SR were categorized into four clusters (cognitive, somatic, atypical, and melancholic), that were constructed and tested before [22]–[25] and are displayed in the supplemental material. The cognitive and somatic symptom clusters were based on DSM-IV criteria

and previous research on these dimensions [25]–[27]. In the somatic cluster, presence of one or more sleep symptoms was counted as one symptom to limit overrepresentation of four sleep symptoms [25]. The algorithm of Novick [24] was used to evaluate the presence of atypical features of MDD based on the DSM-IV criteria, and the algorithm of Khan [23] to determine the presence of melancholic features based on the DSM-IV criteria. A sum score for each cluster was created by adding the dichotomous variables of all individual symptoms per cluster. As a result the cognitive sum score ranged from 0-10, the somatic sum score from 0-7, the atypical sum score from 0-5 and melancholic sum score from 0-8.

Statistical analyses

We compared baseline characteristics for MDD patients with MS and without MS by performing chi-squared comparisons for dichotomous variables and one-way analyses of variance (ANOVA) for continuous variables. Using linear regression analysis, within the MS sample we examined whether MS characteristics were associated with depression severity. Percentages and chi-squared statistics for the presence of individual depressive symptoms were presented for both groups. To examine whether MS was associated with the presence of individual depressive symptoms, logistic regression analyses were performed for all depressive symptoms separately in which the presence of each symptom (yes or no) was the dependent variable. Confounders were taken into account by testing two models: unadjusted and adjusted for gender and age. For the symptoms 'appetite disturbance' and 'weight disturbance' (three categories each) multinomial logistic regression analyses were conducted, using the same two models. We used analysis of co-variance (ANCOVA), adjusting for the same confounders, to analyse differences in symptom cluster sum scores. Because of the potential effect of antidepressants on clinical presentation of MDD, in sensitivity analyses we additionally adjusted for antidepressant use. A p-value <.05 was considered statistically significant. All analyses were conducted using SPSS20 for Windows.

RESULTS

Patient and depression characteristics

Descriptive characteristics of the samples are presented in Table 3.1. The MS sample was older and consisted of more women compared with the sample without MS. In the MS sample, time since MS diagnosis ranged from 0.5 to 37 years (median=10 years). The majority of MS patients (61%) had the relapsing-remitting type of MS. Fifty-five percent had low to moderate physical complaints, and 42% severe or very severe physical complaints. More than one third used disease modifying medication, and 58% received symptom relief medication.

With regard to depression characteristics, no difference in depression severity was found between MDD patients with and without MS. MS patients reported an older age of MDD onset, and were less than half as likely to receive antidepressant treatment. MS patients had no comorbid dysthymia, and were less likely to have a comorbid anxiety disorder. More specifically, patients

with MS were less likely to have panic disorder (with or without agoraphobia), and generalized anxiety disorder. There were no differences in the presence of comorbid social phobia and agoraphobia.

The association between general and MS-related factors (MS onset, course, severity, medication) and depression severity within the MS sample is displayed in Table 3.2. None were associated with depression severity.

Table 3.1 Socio-demographics and clinical characteristics for patients with current Major Depressive Disorder and MS versus no MS.

	MS (*n*=83) *mean (SD) or %*	**No MS (*n*=782) *mean (SD) or %***	***p*-value**
Demographics			
Sex, female	85.5	67.4	.001**
Age, years	47.6 (11.1)	41.2 (12.1)	<.001***
Education[a]			.290
Low	2.4	5.9	
Middle	47.0	50.0	
High	50.6	44.1	
Depression Characteristics			
Experiencing First Episode (MDD)	54.2	50.3	.493
Age of onset (MDD)	32.5 (13.7)	26.8 (12.6)	<.001***
Depression severity (IDS)	37.8 (7.1)	38.5(8.7)	.405
Comorbid Disorders			
Dysthymia	0	29.0	<.001***
Anxiety Disorder	37.3	71.5	<.001***
Panic Disorder			
Agoraphobia	0	13.8	<.001***
No Agoraphobia	0	25.8	<.001***
Social Phobia	32.5	40.2	.177
Generalized Anxiety Disorder	1.2	34.7	<.001***
Agoraphobia	7.2	9.8	.441
Anti-depressants use	20.5	49.9	<.001***
MS characteristics			
MS-Medication		NA	NA
Disease modifying (*n*=67)	34.3		
Symptom Relief (*n*=67)	58.2		
Years since MS onset	10.9 (8.6)	NA	NA
(median; interquartile range)	10.0 (3-16.0)		

Table 3.1 Continued.

	MS (*n*=83) *mean (SD) or %*	No MS (*n*=782) *mean (SD) or %*	*p*-value
MS diagnosis by neurologist		NA	NA
Relapsing-remitting	61.3		
Secondary progressive	26.3		
Primary Progressive	6.3		
Relapsing Progressive	6.3		
EDSS[b]		NA	NA
0–1,5	2.4		
2–4	55.4		
4,5–6	16.9		
≥ 6,5	25.3		

** $p<.01$; *** $p<.001$; MS = Multiple Sclerosis; MDD = Major Depressive Disorder; SD = Standard Deviation; IDS-SR = Inventory of Depressive Symptoms; EDSS = Expanded Disability Status Scale; NA = Not Applicable.
[a] Low: elementary education, Middle: lower vocational education, general intermediate education, intermediate vocational education, general secondary education, High: higher vocational education, college education or university; [b] 0-1.5: no complaints, 2-4: low to moderate complaints, 4-6: moderate to severe complaints, ≥6.5: very severe complaints.

Table 3.2 Associations for MS-specific factors and depression severity for MS patients (*n*=83).

	Depression severity (IDS-SR)	
	B (95%CI)	***p*-value**
General determinants		
Sex	-0.53 (-4.99–3.92)	.813
Age	0.08 (-0.06–0.22)	.270
MS-specific determinants		
Years since MS onset	0.09 (-0.09–0.27)	.328
MS type		
Relapsing-remitting [ref]		
Secondary progressive	-0.41 (-3.98–3.16)	.820
Primary Progressive	-0.07 (-6.49–6.36)	.984
Relapsing Progressive	5.14 (-1.29–11.56)	.115
Severity		
No complaints [ref]		
Low to moderate	0.24 (-10.11–10.59)	.963
Moderate to severe	0.29 (-10.55–11.12)	.958
Very severe	2.43 (-8.18–13.04)	.650
Disease modifying medication	2.21 (-1.33–5.75)	.216
Symptom Relief medication	-2.00 (-5.41–1.42)	.247

MS = Multiple Sclerosis; IDS-SR = Inventory of Depressive Symptoms; Ref = Reference Group.

Table 3.3 Frequencies, Chi-squared statistics, regression analyses, and *p*-values for individual depressive symptoms, and ANOVAs and ANCOVAs for sum scores of cognitive, somatic, atypical and melancholic symptom clusters of patients with Major Depressive Disorder and MS and without MS.

	MS		No MS					
	n	**%**	***n***	**%**	***p*[a]**	**OR**	**95%CI**	***p*[b]**
Cognitive symptoms								
Diminished interest in people/activities	24	28.9	263	33.7	.381	0.88	(0.53–1.46)	.612
Feeling sad	53	63.9	481	61.5	.676	1.15	(0.71–1.86)	.576
Diminished quality of mood	44	53.0	458	58.9	.304	0.98	(0.61–1.56)	.929
Concentration/decision making problems	36	43.4	426	54.7	.049*	0.66	(0.41–1.05)	.077
Feeling irritable	38	45.8	425	54.6	.124	0.79	(0.50–1.25)	.314
Interpersonal sensitivity	31	37.3	370	47.4	.082	0.72	(0.45–1.17)	.184
Self-criticism and blame	43	51.8	396	51.1	.902	1.21	(0.76–1.92)	.430
Suicidal thoughts	23	27.7	194	25.0	.589	1.20	(0.71–2.02)	.491
Reduced interest in sex	40	48.2	356	46.1	.718	0.76	(0.47–1.22)	.252
Diminished capacity for pleasure or enjoyment	16	19.3	266	34.1	.006**	0.44	(0.24–0.78)	.005**
Somatic symptoms								
Problems falling asleep	46	55.4	400	51.2	.466	1.31	(0.82–2.09)	.254
Problems sleeping during the night	55	66.3	388	49.9	.005**	1.59	(0.97–2.60)	.065
Early morning awakening	31	37.3	218	28.3	.087	1.20	(0.74–1.97)	.462
Sleeping too much	12	14.5	140	18.1	.413	0.97	(0.50–1.88)	.933
Leaden paralysis	70	84.3	581	74.3	.044*	1.62	(0.87–3.03)	.129
Appetite disturbance[c]					.029*			
Decrease in appetite	8	9.6	105	13.5		0.71	(0.33–1.55)	.388
Increase in appetite	8	9.6	153	19.7		0.40	(0.19–0.85)	.018*

Table 3.3 Continued.

	MS		No MS					
	n	**%**	***n***	**%**	***p*[a]**	**OR**	**95%CI**	***p*[b]**
Weight disturbance[c]					.754			
Weight loss	11	13.3	126	16.2		0.84	(0.42–1.67)	.616
Weight gain	16	19.3	136	17.5		0.90	(0.49–1.64)	.723
Low energy level/fatigability	59	71.1	545	69.7	.793	0.95	(0.57–1.58)	.841
Psychomotor retardation	42	50.6	329	42.1	.138	1.25	(0.78–1.98)	.354
Psychomotor agitation	33	39.8	329	42.3	.650	0.82	(0.51–1.32)	.421
Other symptoms								
Aches and pains	38	45.8	382	49.0	.573	0.73	(0.46–1.16)	.184
Diurnal variation (worse in the morning)	8	9.6	75	10.1	.905	0.90	(0.41–1.98)	.798
Constipation/diarrhea	29	34.9	227	29.1	.265	1.16	(0.71–1.89)	.556
Arousal symptoms	19	22.9	277	35.5	.021*	0.49	(0.28–0.84)	.009**
Future pessimism	40	48.2	289	37.1	.049*	1.62	(1.02–2.59)	.043*
Diminished response of mood	18	21.7	243	31.2	.074	0.58	(0.33–1.01)	.056
Feeling anxious or tense	39	47.0	452	57.9	.055	0.67	(0.42–1.07)	.093
Panic/phobic symptoms	20	24.1	322	41.3	.002**	0.49	(0.29–0.84)	.009**

Cluster sum scores		**mean (SD)**		**mean (SD)**		**mean (SE)**	**mean (SE)**	
Cognitive symptoms	83	4.19 (2.13)	747	4.69 (2.19)	.052	4.29 (0.25)	4.68 (0.08)	.133
Somatic symptoms	83	3.92 (1.22)	763	3.78 (1.40)	.355	3.81 (0.15)	3.79 (0.05)	.930
Atypical symptoms	83	2.06 (0.93)	763	2.05 (1.02)	.923	2.07 (0.11)	2.05 (0.04)	.923
Melancholic symptoms	83	2.55 (1.43)	713	2.81 (1.46)	.136	2.57 (0.16)	2.80 (0.05)	.178

* $p<.05$; ** $p<.01$; SD = Standard Deviation; SE = Standard Error.

[a] Unadjusted; [b] Adjusted for age, sex; [c] Multinomial regression analysis.

Individual depressive symptoms

We explored differences in individual symptoms and symptom clusters between MDD patients with and without MS. The odds ratios for the associations between the presence of MS, and all 30 individual depressive symptoms adjusted for gender and age are displayed in Table 3.3 and Figure 3.1. MS-related MDD was associated with the presence of 'future pessimism' (OR=1.62, 95%CI=1.02–2.59), whereas MDD without MS was associated with 'diminished capacity for pleasure or enjoyment' (OR=0.44, 95%CI=0.24–0.78), 'increased appetite' (OR=0.40, 95%CI=0.19–0.85), 'arousal symptoms' (OR=0.49, 95%CI=0.28–0.84) and 'panic/phobic symptoms' (OR=0.49, 95%CI=0.29–0.84). Twenty-five symptoms (83%) out of 30 were not associated with MS including the MDD core symptoms 'feeling sad' and 'diminished interest in people/activities'. All five associations remained present after additional adjustment for antidepressants use.

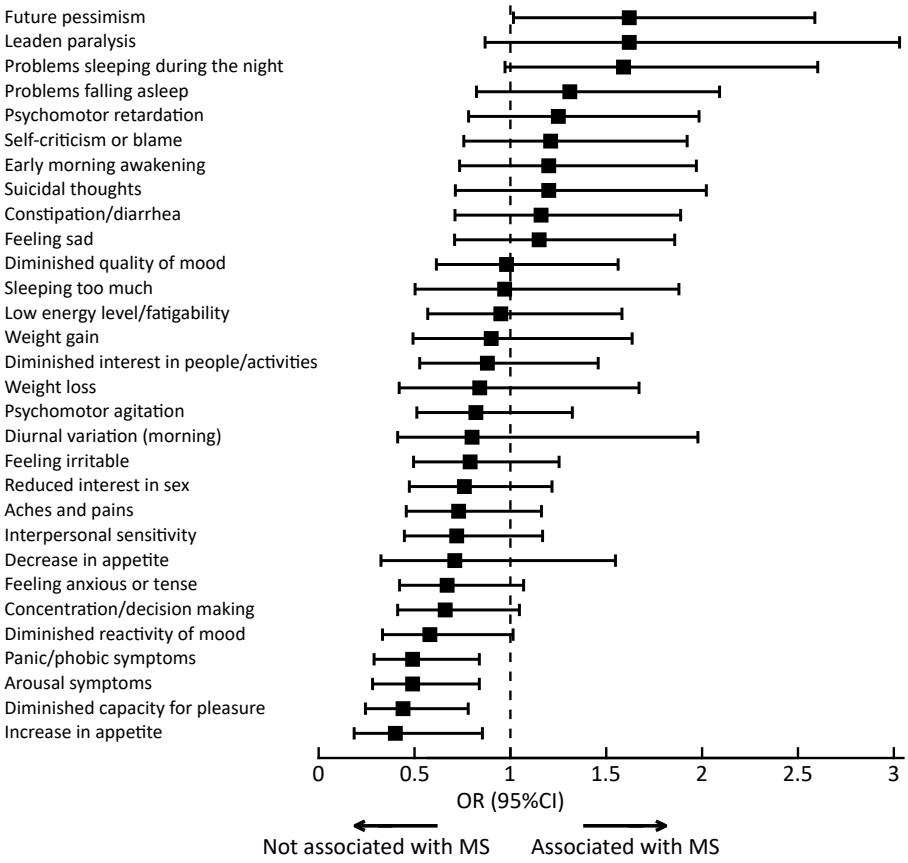

Figure 3.1 Odds ratios (OR) and 95% confidence intervals (CI) for the associations between the presence of MS and individual depressive symptoms adjusted for gender and age. OR<1 indicates the symptom is not associated with MS, OR>1 indicates the symptom is associated with MS.

Symptom clusters

Table 3.3 further shows differences in cognitive, somatic, atypical and melancholic clusters between MDD patients with or without MS. No differences between those with and without MS were found for any of these symptoms clusters, indicating that cognitive, somatic, atypical and melancholic symptoms are unrelated to the presence of MS.

Comorbidity with anxiety

MDD patients with MS were less likely to have a comorbid anxiety disorder and had a smaller amount of panic, phobic and arousal symptoms compared with MDD patients without MS, which suggests diminished anxiety distress in MS-related depression. In order to better understand our differential findings regarding anxiety distress in the MDD profile of patients with and without MS, we additionally explored in what way the anxiety component of depression was involved in both groups.

The DSM-5 includes an anxious distress specifier to acknowledge the clinical importance of anxiety features in MDD [28]. This general marker for anxiety is recently validated by Gaspersz *et al.* [29], who constructed the specifier by selecting five items from the IDS-SR [15] and the Beck Anxiety Inventory (BAI) [30] that matched the five involved DSM-5 criteria (see supplemental material). MDD patients with the DSM-5 anxious distress component showed more chronicity and comorbid anxiety disorders [29]. We constructed the specifier of Gaspersz [29] by counting the number out of five dichotomous IDS and BAI symptoms present and performed an ANCOVA correcting for age and gender. MDD patients with MS showed indeed diminished anxious distress according to the specifier (M=2.05 (SE=0.15) versus M=2.39 (SE=0.05), p=.035) indicating their MDD profile to differ in the DSM-5 anxious distress component.

CONCLUSION

This study demonstrates that the symptom profile of moderate or severe MDD in MS patients is quite similar compared with the profile of moderate or severe MDD in patients without MS, and both cognitive and somatic symptoms are equally present. Subtle differences indicate future pessimism to be more common in MS-related depression, whereas anhedonia is more typical for MDD patients without MS. The core depressive symptoms (sadness and loss of interest), depression severity and symptom clusters of MDD are not different in MS patients, and do not distinguish them from MDD patients without MS. However, MS-related MDD is characterized with a later onset, less comorbid dysthymia, panic and generalized anxiety disorders, and with diminished anxiety distress.

Our findings suggest that the presence of MS or a direct pathophysiological aetiology does not inflate the number of somatic symptoms or change the clinical MDD profile found in those without MS. Not only is the MDD profile similar in MS and no-MS patients, it also seems a stable concept within the MS group itself as MS characteristics were not associated with depression severity. The aetiological underlying mechanisms of MDD in MS might be similar or overlapping

with that of many psychiatric MDD patients, as damage to the hippocampus, HPA-hyperactivity and elevated inflammatory markers are found to be present in both groups [7],[8],[31].

Our results are largely in line with a recent study also showing a similar clinical phenotype of depression in depressed patients with and without MS, using a commonly used self-report questionnaire [11]. Our study does not only replicate these findings, but also provides extended evidence for the view that depression is a similar concept in patients with and without MS by showing that a similar profile is also found when assessing MDD with a diagnostic interview, and irrespective of antidepressant usage. These findings further support the suggestion that self-report measurements for depression, comprising symptoms that overlap with MS symptoms, are accurate to assess depression in MS [32].

Although we demonstrated most depressive symptoms to be common in MS-related MDD, we cannot test whether these symptoms are independent of MS itself. Considering our findings of similar depression profiles in MS and no-MS patients, we would however suggest clinicians to pay attention to all components of depression when making a diagnosis. To avoid misinterpretation of overlapping MS symptoms as depressive symptoms, one might consider asking MS patients with MS specific complaints about their mood and other depressive symptoms as MDD patients seem to experience the same kind of symptoms and difficulties regardless of presence of MS.

MS-related depression was characterized by later onset, and less comorbid dysthymia and anxiety disorders. The low level of comorbidity is a remarkable finding as one would expect considerable elevated dysthymia and anxiety in severe MDD. While the prevalence rates of anxiety disorders in MS vary widely (1%-36%) [1], anxiety in MS seems higher (8.7%-22%) compared to a matched population (8.7%-5.1%) [2]. Although our finding on reduced comorbid anxiety in MS-related MDD needs replication, some speculations can be made. First, when early age of onset and comorbidity are associated with an unfavorable prognosis, MS patients with MDD might concern a subset of less typical psychiatric patients in whom genetic vulnerability and developmental aspects play a smaller role [12]. In addition, MDD in MS patients might present itself as a non-anxious MDD that often stands on its own due to the presence of a brain disease with specific MS-related brain abnormalities related to MDD, and not anxiety. It has been proposed that there is no association between anxiety and either MRI abnormalities or clinical variables in MS, suggesting anxiety to be a reactive response to the psychosocial pressure on patients and not related to the disease itself [33]. If so, and assuming that a partly distinct neurobiology may underlie comorbid MDD and anxiety versus MDD alone [34], studying the neurobiological correlates of MS-related MDD might contribute to increased understanding of the pathogenesis of pure MDD in general.

In order to shed more light on the prognosis, comorbidity and profile of MS-related MDD, investigation of personality might be of use since depression is strongly linked to personality characteristics as higher neuroticism, and lower levels of conscientiousness and extraversion [35]. However, we did not examine personality traits in our sample which can be viewed as a limitation of our study. Another limitation is that data were obtained from two different studies that were not fully compatible, and analyses were based on cross-sectional data hampering conclusions on the development of depressive symptoms within patients over time.

Besides the differences concerning comorbid anxiety and dysthymia, only subtle differences in depression symptomatology existed between depressed patients with and without MS. Depression's core symptoms and symptom clusters were not different between the two groups. This suggests that the clinical profile of depression remains valid among MS patients and that the signs, symptoms and also the instruments to measure depression that have been developed in mental health can be used among MS patients.

Acknowledgements

The randomized controlled trial was supported by 'Stichting MS Reseach' (Grant number 09-678). The infrastructure for the NESDA study (www.nesda.nl) has been funded through the Geestkracht program of the Netherlands Organisation for Health Research and Development (Zon-Mw, grant number 10-000-1002) and participating universities (VU University Medical Center, Leiden University Medical Center, University Medical Center Groningen).

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Supplementary Material 3.A Depressive symptom clusters and DSM-V anxious distress specifier.

The *cognitive cluster:* includes the symptoms 'feeling sad', 'feeling irritable', 'the quality of your mood', 'concentration/decision making', 'view of myself', 'thoughts of death or suicide', 'general interest', 'capacity for pleasure or enjoyment (excluding sex)', 'interest in sex', and 'interpersonal sensitivity'.

The *somatic cluster:* consists of the symptoms 'decreased or increased appetite', 'deceased or increased weight', 'energy level', 'feeling slowed down', 'feeling restless', leaden paralysis/physical', and four items on sleep 'falling asleep', 'sleep during the night', 'waking up to early', 'sleeping too much'.

The *atypical cluster*: includes the symptoms 'having mood reactivity', 'hyperphagia', 'hypersomnia', 'leaden paralyses' and 'interpersonal rejection'.

The *melancholic cluster*: consists of the symptoms 'lacking mood reactivity' and 'loss of pleasure', 'distinct quality of depressed mood', 'mood worsening in the morning', 'early morning awakening of at least one hour before usual time', 'psychomotor retardation or 'agitation', 'significant anorexia or weight loss', and 'excessive or inappropriate guilt'.

DSM-5 anxious distress specifier: consist of the Inventory of depressive symptoms (IDS-SR) items 'Feeling anxious or tense' (criterion 1), 'Feeling restless' (criterion 2), 'Concentration/decision making' (criterion 3), and the Beck anxiety inventory (BAI) items 'Fear of worst happening' (criterion 4) and item 14 'Fear of losing control' (criterion 5).

4

A COMPUTER-BASED SCREENING METHOD FOR DISTRESS IN PATIENTS WITH MULTIPLE SCLEROSIS: A FEASIBILITY STUDY

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JMIR Research Protocols. 2014; 3(2):e29.

ABSTRACT

Background: In multiple sclerosis (MS) patients, symptoms of anxiety, depression, pain, and cognitive impairment are highly prevalent and contribute to lower wellbeing. As these physical and psychological symptoms of distress often stay unnoticed, regular screening could offer possibilities to identify and refer impaired patients to appropriate care.

Objective: The aim of our study was to pilot a new computer-based method in 43 MS patients to efficiently screen for a variety of psychological and physical symptoms of distress.

Methods: Data on feasibility and psychological and physical distress (anxiety, depression, fatigue, physical disability, cognitive functioning) were collected via a touch screen computer. Referral to psychosocial care and rehabilitation was retrospectively checked.

Results: The results demonstrated that most patients considered the screening meaningful (*n*=35/40, 88%) and the system easily usable (*n*=37/40, 93%). Average completion time of the screening was below 8 minutes. Many patients (*n*=35/40, 88%) had elevated distress levels, of whom the majority was referred.

Conclusions: These findings imply that computer-based screening for MS-related distress incorporated in clinical-care is feasible and aids to identify psychological or physical needs. A randomized controlled trial with follow-up should address whether this screening method could be more effective than routine care, and whether it can improve costs and efficiency of care.

INTRODUCTION

Multiple Sclerosis (MS) is a chronic inflammatory disease of the central nervous system that can have a great impact on a patient's life. In multiple sclerosis patients, symptoms such as depression, anxiety, fatigue, pain, and cognitive dysfunction, are highly prevalent both in early and more advanced disease stages and related to lower quality of life [1]–[3]. In the present study, we focus on this wide variety of physical and psychological symptoms impairing MS patients in their daily activities, and refer to them with the umbrella term "distress". Although treatments are available that can help to minimize some of these symptoms, still much distress remains unrecognized and untreated [2],[4]. Consequently, it has been recommended that, with each visit to the neurologist or clinic, neurological nurses should screen and evaluate the level of distress in MS patients [5].

In clinical care, routine screening techniques can help to enable adequate recognition of distress and referral to appropriate care. Lately, successful initiatives of computer-assisted data collection in health care have increased. Advantages are high compliance rates, rapid completion and processing, and immediately available results [6]–[11]. The aim of the present study was to pilot a computer-based screening method, which can be easily incorporated into clinical care to support MS nurses in identifying psychological or physical needs of MS patients.

METHODS

Patients and procedure

From February to August 2012, consecutive MS patients who visited the MS nurse of the Department of Neurology of the VU University Medical Center in Amsterdam, the Netherlands, were asked to complete a computer-based screening with six self-report questionnaires. Patients were mainly referred to the MS nurse by their neurologist after their first visit, a standard procedure for patients who remain under our care, or could make a request for consultation themselves. Consultation with the MS nurse was aimed at getting acquainted, providing information on MS and treatment, and discussing further assistance if required.

One week before the visit, patients were invited by telephone and letter to participate in the pilot. Fifteen minutes before the consultation, nursing staff assisted the patient to the touchscreen computer in a private room to fill out the questionnaires. The patient identification number was filled in, which was linked with the hospital database that contains general data on patients' age, gender, and disease history. Then, questions on psychological and physical distress followed by questions on satisfaction about the screening procedure were presented to the patient on the computer screen one by one (Figure 4.1). Patients answered by touching the appropriate response on the screen and then moved on to the next question. More details of the software and computer system have been described elsewhere [9].

Figure 4.1 Screenshot of one of the questions of the Hospital Anxiety and Depression Scale as presented to the patient on the touchscreen (translated from Dutch to English).

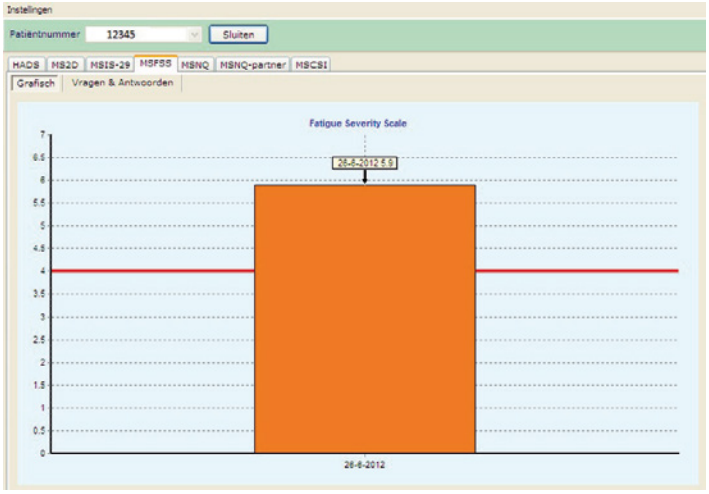

Figure 4.2 Screenshot of the patient score on one of the questionnaires (Fatigue Severity Scale) as presented to the nurse. The red line indicates the cut-off value.

When patients finished the screening, they were assisted to visit the MS nurse in another room. By using the patient identification number, the nurse had direct access to the results that were displayed in graphs on her computer screen (Figure 4.2). At the end of the pilot project, the MS nurse was asked to evaluate the screening.

Measures

Feasibility

Compliance rate and time needed to complete the questions were recorded. Patient satisfaction regarding the system and procedure was evaluated by seven self-designed questions and a 10-point visual analogue scale (VAS). Also the MS nurse was presented with comparable questions of satisfaction on paper.

Distress

We used questionnaires that have been shown to be reliable, valid, and frequently used in clinical practice and/or research in MS. Clinical relevant cut-offs based on literature or clinical practice were used for all questionnaires. Anxiety and depression were measured with the Hospital Anxiety and Depression Scale (HADS, each subscale cut-off>7) [12], fatigue with the Fatigue Severity Scale (FSS, cut-off≥4) [13], and cognitive functioning with the Multiple Sclerosis Neurological Questionnaire (MSNQ, cut-off>27) [14]. The Multiple Sclerosis Impact Scale-29 (MSIS-29) was used to explore the impact of MS on physical (cut-off>60) and psychological wellbeing (cut-off>24) [15]. Finally, patients were asked to fill in the VAS health thermometer from the EuroQol-5D (EQ-5D). The EQ VAS self-rating records the respondents' own assessment of their health status on a vertical VAS where the endpoints are labeled "best imaginable health state" (100) and "worst imaginable health state (0)" [16].

Referral

Several weeks after the consultation, we explored patients' medical files and retrospectively coded referrals to social workers, psychologists, physiatrists, physiotherapists, and occupational therapists.

RESULTS

Feasibility

Of the 43 referred patients, 2 patients did not give consent for scientific documentation and 1 was excluded because he was physically unable to complete the screening questionnaires. It took the 40 remaining patients on average 7.4 minutes (median=6.8, interquartile range= 3.1) to complete the 66 questions on distress. This was evaluated as "little time" by 36 of 40 patients (90%) and the majority (*n*=37/40, 93%) reported that the equipment was easy to use and experienced the screening as meaningful (*n*=35/40, 88%). On average, the screening was graded 7.5 (range 3-10, *n*=38).

The MS nurse evaluated the screening positive on the VAS (7.5). She was satisfied with the quality and content, the system was easy to use and it took her little time to consult the screening data. The screening facilitated her work and helped her to more specifically focus on actual problems to be addressed, including unmentioned problems that could be overlooked easily.

Outcome Measures

For the total group (*n*=40), the mean HADS-score for anxiety was 8.3 (SD=3.6) and depression 5.4 (SD=3.8). Mean FSS and total MSIS-29 scores were 5.0 (SD=1.6) and 67.7 (SD=25.3), respectively. Mean MSNQ-score was 23.4 (SD=12.2). On average, patients gave their general health 66 (SD=17.7) points out of 100. A large part of patients (*n*=35/40, 88%) had scores above cut-off, indicating high levels of distress. More specifically, Figure 4.3 shows that 21 of 40 patients (53%) met criteria for anxiety. A remarkably lower percentage of patients met the criteria for depression (*n*=10/40, 25%). Fourteen of 40 patients (35%) had significant cognitive complaints, 10 of 40 patients (25%) experienced a high physical impact of MS, and 28 of 40 patients (70%) met criteria for significant fatigue.

Referral

Some patients reported already suitable treatment for their distress. However, Table 4.1 shows that the majority was referred by the MS nurse to psychosocial care or rehabilitation.

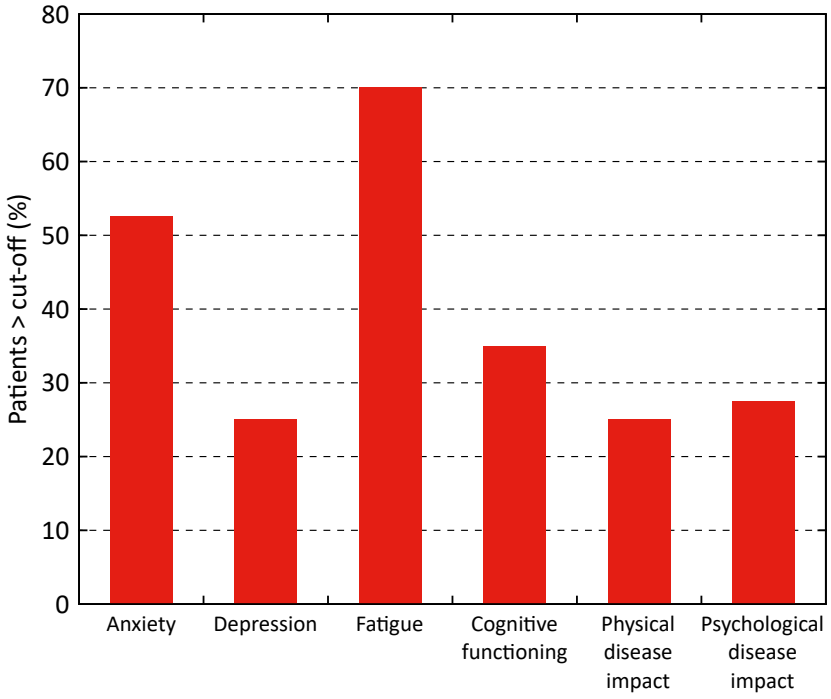

Figure 4.3 Percentage of MS patients (n=40) with high level of psychological or physical distress.

Table 4.1 Percentage referred and treated MS patients with low and high level of distress.

	HADS[a]		MSIS-29[b]		FSS[c]		MSNQ[d]	
	<cut off (n=18), %	>cut off (n=22), %	<cut off (n=25), %	>cut off (n=15), %	<cut off (n=12), %	>cut off (n=28), %	<cut off (n=26), %	>cut off (n=14), %
No referral	28	18	32	7	34	18	31	7
Suitable care	17	14	12	20	8	14	19	0
Referral	55	68	56	73	58	68	50	93
Referral only	17	18	16	20	8	25	15	29
Treatment after referral	38	50	40	53	50	43	35	64

[a] Hospital Anxiety and Depression Scale, measures anxiety and depression; [b] Multiple Sclerosis Impact Scale-29, measures Physical and Psychological disease impact; [c] Fatigue Severity Scale, measures fatigue; [d] Multiple Sclerosis Neurological Questionnaire, measures cognitive functioning.

DISCUSSION

Principal Findings

This pilot study shows that computer-based screening is a feasible way to detect psychological and physical distress in MS-patients in clinical care, and could support MS nurses in their work. It constitutes an easy way to administer questionnaires and processing data that can be directly available to patients and nurses. The computer-based method we demonstrated here can be easily adapted for routine screening. It would be suitable for application on personal mobile devices or via an Internet website, offering patients the possibility to complete it in their own time and pace, improving costs and efficiency of care.

Regular screening offers possibilities to identify and refer impaired patients to appropriate care as early as possible and monitor distress. Also, screening could increase patient awareness that their experienced distress can be related to MS, which might decrease barriers to request appropriate treatment. Next to clinical use, data collection could be suitable for scientific documentation.

Conclusions

MS patients appear to be willing to complete a computer-based screening. Average completion time of our assessment was comparable with similar initiatives (5–8.7 minutes) [6-8]. Many patients showed elevated levels of distress, and were referred to further care. However, the number of referred patients with minimal distress was disproportionally high. Moreover, the results do not provide us with a complete overview of prescribed medication and referrals other than psychosocial and revalidation care. In addition, whether relevant needs of MS patients are covered by this procedure is still unclear because our study concerns a pilot design using an uncontrolled unselected sample. Therefore, the findings of this study should be used with

caution. A randomized controlled trial with longer follow-up should reveal whether routine screening, in comparison to routine care, is effective in detecting distress that would otherwise remain unnoticed, and results in appropriate referrals, adequate treatments, and improved distress outcomes.

Acknowledgements

This work was supported by 'Fonds NutsOhra' (Grant number 0904-58). The authors thank I. M. Verdonck-de Leeuw and A. Houffelaar for their contribution to the project.

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5

FEASIBILITY AND OUTCOME OF A WEB-BASED SELF-HELP INTERVENTION FOR DEPRESSIVE SYMPTOMS IN PATIENTS WITH MULTIPLE SCLEROSIS: A PILOT STUDY

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Journal of the Neurological Sciences. 2012; 315(1):104–109.

ABSTRACT

Background: Depressive symptoms are highly prevalent among patients with multiple sclerosis (MS). Web-based problem-solving therapy (PST) is easily accessible and showed to be effective in depressed patients.

Objectives: The aims of this pilot study were to examine feasibility and outcome (reduction of depressive symptoms) of an applied web-based PST intervention in MS patients.

Methods: Forty-four MS patients with mild to severe depressive symptoms followed a web-based PST intervention. Feasibility was measured by compliance rate and satisfaction scales. The Beck Depression Inventory (BDI-II) was used to measure depressive symptoms before and after the intervention.

Results: The compliance rate was 52%, and 85% of the patients rated the quality of the intervention as good or excellent. After the intervention, depressive symptoms had significantly decreased (BDI-II change: mean=-3.9, p=.01, d=0.51 in intention-to-treat analysis; BDI-II change: mean=-9.0, p<.001, d=1.50 in completers analysis).

Conclusions: This study suggests that applied web-based PST is feasible and reduces depressive symptoms in MS patients. Especially MS patients who experience disease-related or other barriers to participate in face-to-face counselling could benefit. However, ways to increase compliance should be considered. A randomized controlled trial is recommended to more extensively investigate effectiveness of this intervention in treating depressive symptoms in MS patients.

INTRODUCTION

Depressive symptoms are highly prevalent in patients with multiple sclerosis (MS). Lifetime risk for depression in the MS population has been estimated at around 50%, compared with 10-15% in the general population [1],[2]. Depression is related to poorer quality of life, disrupts social support and family systems, and has been associated with fatigue, a cutback in working hours and cognitive impairment in MS patients [1]. The risk of suicide is 2.3 times elevated in the MS population [3], with the most important risk factor for suicide being a depressive episode [4]. Furthermore, depression can result in decreased adherence to MS treatment, which may affect health status adversely [5]. It remains unclear whether depressive symptoms in patients with MS are primarily reactive in nature as a response to the unpredictable and uncertain course of the disease, or whether neurobiological factors play a part [1],[6].

More than half of the cases of depression in MS patients are underdiagnosed [7],[8]. Possible reasons could be that patients perceive their emotional problems as an unsolvable component of the disease process, therefore leaving them unmentioned in the consulting room of the physician. In addition, mental problems are not the primary focus of physicians and general practitioners [9]. Besides, if depressive symptoms are recognized, adequate treatment often tends to be lacking [1],[10].

A number of clinical trials on cognitive behavior therapy (CBT) have shown that psychotherapy is an effective treatment for depression in patients who suffer from MS [1],[9],[11],[12]. This applies especially to depression treatment that focuses on developing skills to cope with the unpredictable and uncertain course of MS and its consequences [9],[13]. Problem-solving therapy (PST), comprising a cognitive behavioral method, is based on the assumption that psychological symptoms of depression are often caused by (practical) problems people face in their daily lives combined with poor problem-solving skills. PST helps people to solve these problems in a structured way by teaching them more adequate problem-solving skills [14],[15]. Several studies found PST to be effective in the treatment of depression [16],[17]. However, MS patients can experience additional difficulties in attending psychotherapy treatment due to disease-related factors such as fatigue, physical impairments and transportation difficulties. These complicating factors seem to have a major impact on receiving face-to-face treatment [12],[18].

To avoid the aforementioned barriers that hamper ordinary psychotherapeutic treatment, other forms of treatment delivery can be introduced such as brief sessions, therapy by telephone or more self-help orientated alternatives. During the past years there has been a significant increase in the use of telecommunication to provide self-help oriented psychotherapy for a wide range of psychiatric conditions. Recent findings show that CBT provided by telephone or using the Internet is an effective method of treatment for depression in general [19]–[21]. In depressed MS patients, Mohr and colleagues found a significantly larger decrease of depressive symptoms in those receiving a telephone-administered CBT compared to those receiving supportive emotion-focused therapy [18] or no mental healthcare at all [22].

These forms of treatment may result in a reduction of treatment time, commuting time, and treatment costs. Furthermore, they are easily accessible and have the advantage of reaching a

large number of people with functional impairments due to physical health problems. Although web-based CBT has demonstrated to be effective in reducing depressive symptoms, evidence is lacking whether this also applies to depressive symptoms in MS patients.

Therefore, the aim of our pilot study is 1) to explore the feasibility of using the Internet and PST as an alternative treatment opportunity for reducing depressive symptoms in MS patients, and 2) to examine the outcome of the intervention on symptoms of depression and on additional measures of anxiety, quality of life, physical functioning and problem- solving skills. If the web-based PST intervention would turn out to be feasible with a positive outcome, a new treatment for depressive symptoms in MS patients would become within reach.

METHODS

Patients

The VU University Medical Center Amsterdam, the Netherlands, provided a database containing all patients with definite MS who visited the Department of Neurology in 2008. From May to September 2009, 206 MS patients were recruited from this database. Another 31 patients with MS registered for this study through advertisement in MS newsletters, and 23 MS patients were directly referred by their neurologists at the VU Medical Center.

All patients received a mailing with a username and password to fill out an online version of the Beck Depression Inventory (BDI-II) [23],[24], as an initial screening questionnaire on depressive symptoms. Patients were included in the study if they (1) were 18 years or older, (2) scored 16 or higher on the BDI-II and (3) reported a diagnosis of MS confirmed by a neurologist (>3 months ago). Potential participants were excluded if they were currently receiving psychotherapy, did n ot have access to the Internet, were physically unable to attend an online intervention or reported suicidal ideation. A reminder phone-call was used to enhance the response rate.

Flow of patients

Two hundred sixty MS patients received an invitation to fill out the depression screening questionnaire, the response rate was 58% (n=150). Fifty four of the responding MS patients had a mild to severe depression according to their score on the Beck Depression Inventory (BDI-II≥16); the other 96 patients (BDI-II<16), were excluded. Four of the remaining 54 patients were excluded because they were receiving psychotherapy, two were physically unable to attend an online intervention, and four finally refused to participate. The remaining 44 patients consented to participate in the pilot study. Figure 5.1 describes the flow of patients.

Procedures

We conducted a pilot study with one condition. The protocol of the study was approved by the medical-ethical committee of the VU University Medical Center Amsterdam. Patients meeting inclusion criteria received a letter concerning the research, content of the intervention and an informed consent form. After giving informed consent, patients were invited to fill out a set of

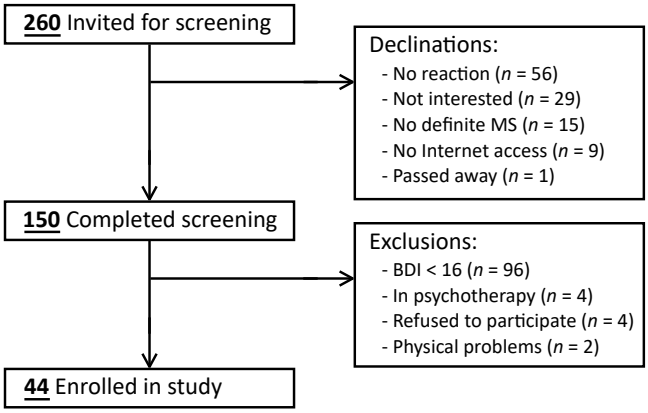

Figure 5.1 Patients flow.

online questionnaires to obtain baseline data. Finally, the depression and anxiety section of the World Health Organization's Composite International Diagnostic Interview (WHO CIDI, 1990) [25] was conducted by telephone. Patients then received a password and username to access the online self-help intervention from their personal computers via the Internet. Inclusion time to the intervention was from April to November 2009. The PST intervention (duration: 5 weeks), is further described in the section 'Intervention'. At completion of the web-based PST intervention, patients filled out the online questionnaires of the post-intervention assessment. The patients who did not complete the intervention received an invitation for the post-intervention assessment 10 weeks after the baseline measurement. Participation in the study did not interfere with the ongoing MS treatment in any way.

MEASURES

Feasibility

Feasibility was measured by compliance rate and a self-designed 10 point Visual Analogue Scale (VAS) to evaluate the opinion of patients about the website, support and the total intervention. We additionally used the Client Satisfaction Questionnaire (CSQ-8) [26] to check whether patients were satisfied with the care they received. The CSQ-8 has a maximum achievable score of 32. For the VAS and the CSQ-8, higher scores indicate more satisfaction.

Outcome

The Beck Depression Inventory [23],[24] was used to measure depressive symptoms. This self-report instrument is the most commonly used measure of depression severity in patients with MS (1), and has shown to be valid and reliable [27],[28]. We used the Beck Depression Inventory

Second Edition (BDI-II) [23] which is the most recent version of the BDI. It consists of 21-items measuring symptoms of depression, such as pessimism, sense of failure, guilt, self-dislike, suicidal ideas, insomnia and weight loss. The total score is calculated as the sum score of all items and ranges 0 to 63. Sum scores of 0–13 represent minimal depressive symptoms, 14–19 mild depression, 20–28 indicate moderate depression and 29–63 severe depression.

A number of additional outcome measures were employed. The anxiety subscale of the Hospital Anxiety and Depression scale (HADS) [29] was used to assess the presence of anxiety symptoms. This scale consists of 7 items, with scores ranging from 0 to 21 with higher scores indicating more anxiety. Since we already used the BDI-II to measure depressive symptoms, the HADS was only used to measure anxiety symptoms. In addition, we used the physical functioning subscale of the Medical Outcome Study Short Form 36 (SF-36) [30] and the EuroQol quality of life measure [31], comprising a five-part questionnaire (EQ-5D) and a visual analogue self-rating scale (EQ-VAS). Patients' problem-solving skills were evaluated by the Social Problem Solving Inventory Revised (SPSI-R) [32]. The SPSI-R consists of the following subscales: Negative and Positive Problem Orientation (NPO, PPO), Rational Problem Solving (RPS), Impulsivity/Carelessness style (ICS) and Avoidance Scale (AS). All questionnaires were administrated via the Internet.

Other variables

A clinical diagnosis of Major Depression Disorder and/or Anxiety Disorder according to DSM-IV-TR criteria was assessed by a telephone interview using the WHO CIDI [25]. Finally, socio-demographic and medical MS data (i.e. year of diagnosis, onset of first symptoms, medication usage, type of MS) were collected by online self-report.

Intervention

The online cognitive-behavioral self-help intervention examined in this study is based on what is known as 'Problem-Solving Therapy' (PST) [14]. We adjusted the original online PST-based intervention for depression as described by Van Straten *et al.* [33] for MS patients with co-morbid depression. Modifications concerned additional information about MS and its psychosocial consequences, and adjustment of text and examples. The intervention consisted of five modules containing text, exercises and examples. Patients were asked to work on one module a week and exercise for at least 2 hours a week. Support during the intervention consisted of communication via the website through brief, weekly e-mails, and was provided by supervised and trained master's clinical psychology students. The e-mail correspondence was intended to facilitate the patient's effective use of the self-help method, and was explicitly not intended to build up a patient–therapist relationship.

Statistical analyses

We compared baseline characteristics for patients who completed the intervention (completers) and patients who did not (non-completers): by performing chi-square comparisons for dichotomous variables and independent *t*-test statistics for continuous variables.

Descriptive statistics of compliance rate and satisfaction were used to explore the feasibility of web-based PST as an alternative treatment opportunity for MS patients with co-morbid depressive symptoms. Paired *t*-tests were performed to assess changes between pre-intervention and post-intervention in order to determine the improvement of patients during the intervention. We used both intention-to-treat (ITT) analyses and completers analyses. In the ITT analyses, the conservative Last Observation Carried Forward method (LOCF) was used to impute data for those who did not complete post-intervention assessments (n=4). To evaluate the magnitude of the improvement of the intervention on outcome measures, effect sizes were calculated for all patients and for completers only, using Cohen's formula [34]. Effect sizes were calculated by subtracting the post-intervention values from the pre-intervention values, divided by the pooled standard deviation. Effect sizes of 0.56 or higher can be assumed to be large, while effect sizes of 0.33–0.55 are moderate, and effect sizes of 0–0.32 are small.

We used the method of Jacobson and Truax [35] to measure the proportion of participants who improved and recovered. The reliable change index (RCI) [35] was used to determine statistically significant change in the BDI-II from pre-intervention to post-intervention, at the level of individual patients. The RCI was determined by subtracting a patients' post-intervention score from the pre-intervention score and dividing it by the standard error of difference between the two test scores. Patients are seen as improved if the RCI is higher than 1.96, since it would be unlikely that this change occurs by chance. A decrease of 3.7 or more on the BDI-II implies in this case statistically reliable change. Finally, recovery from depressive symptoms was defined as reliable change *plus* a score of 13 or lower on the BDI-II [36].

RESULTS

Patients

Baseline characteristics of the 44 enrolled patients are displayed in Table 5.1. Mean age was 45 years and the majority of patients were female (77%) and married (68%). Education level was almost evenly distributed in the study population with 43% lowly educated (<15 years) and 57% highly educated (≥15 years). Time since MS diagnosis ranged from 2 to 40 years (median=5 years). Almost half of the patients (48%) had the relapsing-remitting type of MS, 23% the secondary-progressive type and 18% the primary-progressive type of MS. For 11%, the type of MS was not reported.

Chi-square analyses and analyses of variance revealed no differences in baseline characteristics between patients who completed the intervention and patients who did not, except for the BDI-II. Baseline BDI-II scores of completers were significantly higher compared to non-completers (mean=23 versus mean=17, p=.01).

Table 5.1 Demographic Characteristics.

	All patients (*n*=44)	Completers (*n*=23)	Non-completers (*n*=21)	
Characteristics	**mean (SD) or %**	**mean (SD) or %**	**mean (SD) or %**	***p*-value**
Age, years	45 (12)	46 (11)	45 (13)	.64
Sex, women	77	78	76	.87
Education				.74
Lower	43	48	43	
Higher	57	52	57	
Marital status				.47
Married	68	74	62	
Unmarried	32	26	38	
Years since MS onset				.63
Median (range)	5 (2–40)	5 (2–19)	3 (2–40)	
Type of MS				.24
Relapsing-remitting	48	52	44	
Secondary progressive	23	19	26	
Primary progressive	18	10	26	
Unknown	11	19	4	
MS Medication				
Disease modifying	60 (*n*=40)	61	59 (*n*=17)	.38
Symptom relief	45 (*n*=40)	43	47 (*n*=17)	.72
Psychotropic medication, yes	21	26	14	.33
Diagnose CIDI				.12
Depression	18	11	7	
Anxiety	2	2	0	
Depression & anxiety	10	6	4	
No diagnosis	14	4	10	
BDI-II pre-intervention	20 (7)	23 (7)	17 (7)	.01
HADS pre-intervention	9 (3)	9 (3)	9 (3)	.60
SF36pf pre-intervention	42 (32)	38 (30)	45 (34)	.49
SPSI-R pre-intervention				
PPO	11 (3)	10 (3)	11 (3)	.16
NPO	18 (5)	20 (5)	16 (6)	.06
ICS	17 (5)	17 (5)	16 (5)	.31
RPS	37 (9)	36 (9)	38 (9)	.50
AS	11 (4)	12 (4)	10 (4)	.12
EuroQol pre-intervention				
EQ-5D	0.56 (0.3)	0.58 (0.3)	0.54 (0.3)	.66
EQ-VAS	62 (17)	61 (20)	63 (14)	.75

MS = Multiple Sclerosis; CIDI = Composite International Diagnostic Interview; BDI-II = Beck Depression Inventory, Second Edition; HADS = Hospital Anxiety and Depression Scale; SF36pf = Short Form-36 Physical Functioning Subscale; SPSI-R: PPO = Positive Problem Orientation, NPO = Negative Problem Orientation, ICS = Impulsivity/Carelessness Style, RPS = Rational Problem Solving, AS = Avoidance Style; EQ-5D = EuroQol-5D; EQ-VAS = EuroQol-Visual Analogue Scale; SD = Standard Deviation.

Feasibility

Compliance rate

The compliance rate for the web-based PST intervention was as follows: 91% completed the assignments of module 1, 70% additionally completed module 2, 64% completed module 3, and 52% completed the whole course (none of the patients dropped out between modules 4 and 5). We clustered the reported reasons of non-completers for early termination of the intervention (n=21). For 24%, computer-related problems were the main reason to drop out of the intervention and 14% reported a lack of time and being too busy to finish the intervention. Around 24% stopped the intervention because of psychosocial and environmental problems as job loss, an ended relationship and personal or family matters. Other reasons (24%) were MS related problems as too much pain, illness, being too depressed, the intervention not meeting someone's needs and wanting to finish the intervention in their own time. For 14%, reasons for dropout were unknown.

Satisfaction

The CSQ-8 showed that 85% of the patients (n=40) rated the quality of the web-based intervention as good or excellent. The majority of patients were satisfied with the amount of help they had received (77.5%) and thought the web-based intervention had helped them to deal with their emotional problems (75%). Around 62% reported that the web-based PST had met their needs and 82.5% would recommend this kind of therapy to others. Finally, 60% of the patients would use the same intervention if they needed help again. The mean CSQ-8 score in the total sample was 23.6 (SD=4.8, range=11–31). Patients who completed the intervention expressed greater satisfaction with the intervention than non-completers (mean=26.1 versus mean=20.1, p<.001). Patients gave their opinion about the website, support and total intervention on a self-designed 10 point Visual Analogue Scale. Support from the coach received the highest rank, i.e. 7.7 (SD=1.2), the website scored 7.2 (SD=1.1) and the total intervention scored 7.2 (SD=1.3). Differences in VAS score between completers and non-completers were significant (mean=8.2 versus mean=6.9, p=.002, mean=7.5 versus mean=6.7, p<.05, mean=7.7 versus mean= 6.6, p=.01).

Outcome

ITT and completers analyses

ITT analyses (n=44) revealed a significant reduction in depressive symptoms measured by the BDI-II. Figure 5.2 shows that the mean score of depressive symptoms for all patients decreased from 20.1 to 16.2 with a Cohen's d of 0.51 (p=.01). Completers analyses (n=23) revealed a more pronounced decrease (from 22.8 to 13.8, p<.001) in depressive symptoms on the BDI-II with an effect size of Cohen's d=1.50. After correction for baseline BDI-II scores, there was a significant difference in BDI-II change scores between completers (mean=-7.9) and non-completers (mean=0.61) (p<.001). Post-hoc analyses revealed that patients with a CIDI diagnosis of Major Depression Disorder and/or Anxiety Disorder (n=30) showed a significant reduction of depressive symptoms (mean BDI-II change=-5.5, p=.002), with an effect size of 0.74.

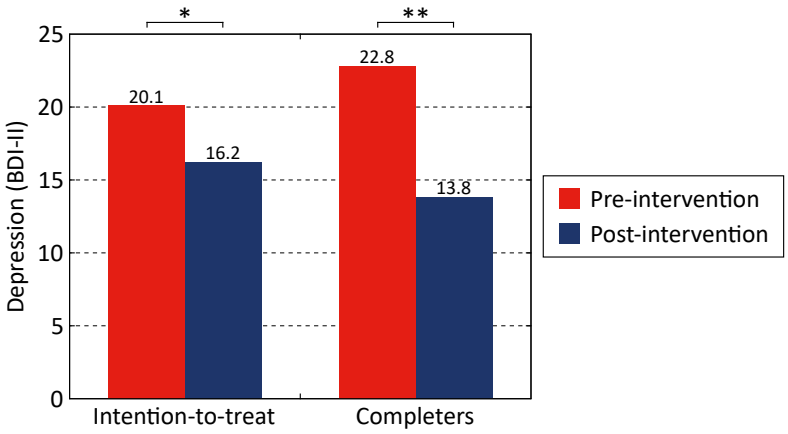

Figure 5.2 Depressive symptoms before and after the web-based intervention (* p=.01, d=0.51; ** p<.001, d=1.5).

Table 5.2 presents mean pre- and post-intervention scores (SD), t-values and effect sizes for additional outcome measures. Completers analyses but not ITT analyses revealed a significant decrease in anxiety measures (p=.004) with a Cohen's d of 0.71. Regarding problem solving skills, the whole sample revealed a decrease in negative problem orientation (p=.004, d=.41), which was larger for patients who completed the intervention (p=.001, d=0.77). Additionally, after the intervention, completers scored higher on positive problem orientation (p=.04) and rational problem solving (p=.02). Finally, the intervention did not seem to have any positive or negative consequence for scores on physical functioning and quality of life scales, and other subscales of the SPSI-R.

Significance for individual patients

Based on the RCI, 47.7% of all patients (n=44) showed a significant improvement in depressive symptoms after the intervention. Seventy-eight percent of the completers (n=23) versus 14% of the non-completers (n=21) met the criteria for reliable change on the BDI-II (χ^2= 18.008, p<.001). Although a large part of patients still scored within the depression range (BDI>13) at post-treatment, about one-third of patients (29.5%) showed a reduction in depressive symptoms. Recovery rate differed between completers (52.2%) and non-completers (4.8%) (χ^2=11.854, p=.001).

Table 5.2 Pre-intervention and post-intervention mean scores, standard deviations (SDs), *p* and *t* values and effect sizes for additional outcome measures.

	ITT (*n*=44)							Completers (*n*=23)						
	Pre-intervention		Post-intervention					Pre-intervention		Post-intervention				
Measure	*mean (SD)*		*mean (SD)*		t	p	d	*mean (SD)*		*mean (SD)*		t	p	d
HADS-A	9.2	(3.2)	8.3	(3.4)	1.74	.09	0.27	9.4	(3.1)	7.2	(3.1)	3.7	.001	0.71
SF36pf	41.5	(32)	41.4	(31.6)	0.79	.94	-0.08	38.3	(30.0)	41.3	(29.2)	-2.08	.05	-0.10
EuroQol														
EQ5D	0.56	(0.3)	0.59	(0.3)	0.86	.40	-0.10	0.57	(0.3)	0.63	(0.2)	-1.37	.18	-0.24
VAS	62.0	(16.9)	63.6	(17.0)	-0.89	.38	-0.09	62.7	(13.9)	65.4	(16.5)	-1.09	.29	-0.06
SPSI-R														
PPO	10.6	(2.7)	10.8	(2.6)	-0.55	.59	-0.08	10.0	(2.6)	11.4	(2.3)	-2.19	.04	-0.29
NPO	18.0	(5.4)	15.6	(6.3)	3.00	.004	0.41	19.5	(4.8)	15.3	(6.0)	3.93	.001	0.78
RPS	36.9	(9.1)	37.1	(11.5)	-0.18	.86	-0.02	36.0	(9.3)	39.7	(11.3)	-2.60	.02	-0.36
ICS	16.5	(4.9)	16.7	(5.4)	-0.38	.71	-0.04	17.2	(4.7)	16.9	(5.3)	0.33	.75	0.06
AS	11.3	(3.9)	10.6	(5.5)	1.01	.32	0.15	12.2	(4.0)	10.3	(6.0)	1.81	.08	0.38

HADS = Hospital Anxiety and Depression Scale; SF36pf = Short Form-36 Physical Functioning Subscale; EQ-5D = EuroQol-5D; EQ-VAS = EuroQol-Visual Analogue Scale; SPSI-R: PPO = Positive Problem Orientation, NPO = Negative Problem Orientation, RPS = Rational Problem Solving, ICS = Impulsivity/Carelessness Style, AS = Avoidance Style.

DISCUSSION

This pilot study provides evidence that an adjusted version of web-based PST is a feasible treatment for depressive symptoms in patients with MS. More than half of the patients (52%) completed the intervention and the majority (85%) reported to be satisfied with this web-based intervention. Furthermore, our preliminary findings indicate that the intervention can reduce depressive symptoms in MS patients, especially in those who report more depressive symptoms at baseline and complete the intervention. Apparently, this subgroup of patients could benefit most from this kind of treatment.

Our findings are in line with previous research that indicates that PST improves depressive symptoms. A recent meta-analysis reported mean pre-PST scores of 24.0 (SD=7.3) and post-PST scores of 11.2 (SD=11.2) on the BDI and BDI-II for depressed participants over eight studies [37]. This is comparable to our observations in completers, although it should be noticed that this meta-analysis was based on studies that were carried out in other (not MS) populations using another form of PST (not web-based). Apart from a decrease in depressive symptoms, we also found the web-based intervention to improve problem solving skills (negative and positive problem orientation and rational problem solving) and reduce anxiety. However, the intervention did not improve the specific problem solving styles of Impulsivity/Carelessness and Avoidance, quality of life and physical functioning.

These results are encouraging since depression in MS patients often goes undiagnosed [7],[8], and if diagnosed, adequate treatment tends to be lacking [1],[10]. The fact that 36% of the responding patients (*n*=150, before inclusion) in our study had mild to severe depressive symptoms, and only four patients were receiving psychotherapy, underscores these findings. With a web-based intervention we might reach the group of un-served MS patients who are in need for suitable, easily-accessible treatment for their depressive complaints. In our study 58% of the approached patients agreed to participate. While this is only part of the target population, this number seems relatively high in comparison to a similar study in diabetes patients [38]. However, of the approached patients who agreed to participate only half completed the intervention.

Although web-based treatment has the advantage of reaching a large number of people, it raises the risk of dropout since this kind of treatment is fully the participant's own responsibility. In web-based self-help treatment, it is much easier to postpone or end treatment when an effect is noticed or when the symptoms become less urgent [39]. Recently, a meta-analysis [40] suggests that people with less severe psychological difficulties were more likely to dropout of web-based treatment which is consistent with our finding that patients with less depressive symptoms at baseline were more prone to drop out of the intervention than those with a higher baseline level of depressive symptoms. We compared the compliance rate in this study with other studies examining a similar web-based PST intervention (Figure 5.3). The compliance rate of our study (52%) was comparable to the compliance rates found in those studies (55% [33] and 38% [15]). In addition, a recent meta-analysis found no differences in dropout rates between face-to-face psychotherapy and guided web-based self-help [21]. However, high dropout percentages from web-based interventions have been identified as a major challenge in e-health interventions [41].

Additional research would be needed to understand and prevent dropout in (future) web-based treatment [40]. As reasons for early termination of the intervention, our patients reported computer related problems, a lack of time or being too busy. This is in line with several qualitative investigations of patient's reasons for dropping out of web-based treatment [40]. Still, little is known about the specific factors that could increase compliance rate [42].

Attempts to reduce dropouts contain for example modification of the intervention and sending postcard reminders or adding phone calls [43]. Recently, Mohr and colleagues [42] executed a single-arm feasibility trial to investigate the feasibility of a multimodal e-mental health treatment for depressed patients and suggested that joint effects of internet and telephone administered treatment for depression are promising. In order to further increase the compliance rate, telephone support could be considered in addition to, or instead of, email support [15],[44]. More support or time to practice with the website before the start of the intervention could reduce dropouts in the beginning due to start up problems.

Although the outcome of the web-based intervention seems to be promising, further research should include a control condition to confirm that the observed improvement does not represent the natural course of depressive symptoms in patients with MS. However, several studies have shown that depression in MS patients appears to be stable over time and does not diminish automatically without treatment [45],[46]. A randomized controlled trial with a longer follow-up and a larger sample size is necessary to determine whether the web-based PST intervention is indeed more effective than MS care as usual and to assess it's consequences in the long term. In our study, MS diagnoses were obtained by self report on medical data and not checked afterwards with the neurologist. As a result, MS diagnosis was unknown for 11% of the patients. A written confirmation of the diagnosis from the patient's neurologist would enhance reliability. Finally,

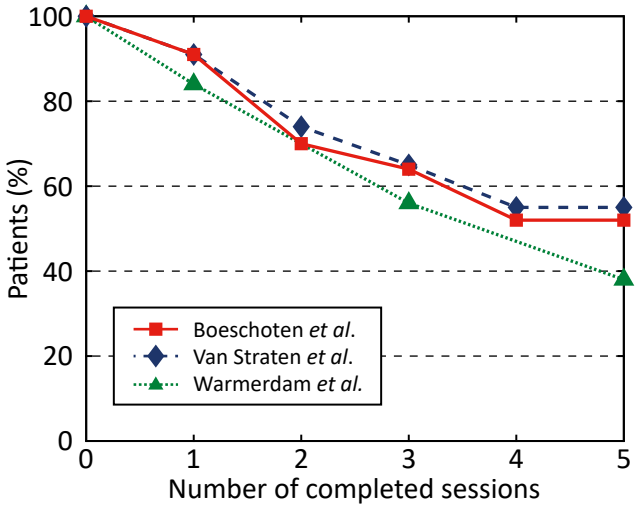

Figure 5.3 Compliance rate of the web-based intervention compared with similar interventions.

cognitive behavior therapy for depressive symptoms has shown to also reduce fatigue symptoms in MS patients [47]. In line with this, web-based PST for depression could improve both depressive and fatigue complaints in MS patients. It would therefore be interesting to additionally examine fatigue measures as outcome.

In conclusion, the results of this pilot study are encouraging and support the initiation of a randomized controlled trial to more elaborately investigate the effectiveness of a web-based PST intervention for depressed MS patients. This intervention could especially benefit those who experience disease-related or other barriers to participation in face-to-face counselling. With an easily accessible, cost-effective web-based self-help intervention we can reach and treat many MS patients with depressive symptoms and improve the quality of care.

Acknowledgements

This work was supported by Stichting MS Research (grant number 08-651 MS) and Stichting tot Steun VCVGZ (grant number ST2688.Me3).

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6

INTERNET-BASED SELF-HELP TREATMENT FOR DEPRESSION IN MULTIPLE SCLEROSIS: STUDY PROTOCOL OF A RANDOMIZED CONTROLLED TRIAL

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BMC Psychiatry. 2012; 12:137.

ABSTRACT

Background: Depression in MS patients is frequent but often not treated adequately. An important underlying factor may be physical limitations that preclude face-to-face contact. Internet-based treatment showed to be effective for depressive symptoms in general and could thus be a promising tool for treatment in MS.

Methods/Design: Here, we present a study protocol to investigate the effectiveness of a 5 week Internet-based self-help problem solving treatment (PST) for depressive symptoms in MS patients in a randomized controlled trial. We aim to include 166 MS patients with moderate to severe depressive symptoms who will be randomly assigned to an Internet-based intervention (with or without supportive text-messages) or waiting list control group. The primary outcome is the change in depressive symptoms defined by a change in the sum score on the Beck Depression Inventory (BDI-II). Secondary outcomes will include measures of anxiety, fatigue, cognitive functioning, physical and psychological impact of MS, quality of life, problem solving skills, social support, mastery, satisfaction and compliance rate. Assessments will take place at baseline (T0), within a week after the intervention (T1), at four months (T2) and at ten months follow-up (T3: only the intervention group). The control group will be measured at the same moments in time. Analysis will be based on the intention-to-treat principle.

Discussion: If shown to be effective, Internet-based PST will offer new possibilities to reach and treat MS patients with depressive symptoms and to improve the quality of care.

Trial Registration: Nederlands Trial Register (NTR2772)

INTRODUCTION

Multiple Sclerosis (MS) is a chronic and progressive inflammatory autoimmune disorder of the central nervous system. MS is a relatively common disease -affecting approximately 1–2 per 1000 individuals- and mainly commences in early to middle adult life. MS patients suffer from a variety of neurological symptoms such as fatigue, poor balance, impaired speech, bladder and bowel dysfunction, weakness, pain, spasms, cognitive deficits [1],[2].

Lifetime risks for depressive disorders in MS patients are high (~50%) [3]. Findings thus far indicate that depression seems more severe and common in MS compared with healthy people. However, due to overlap of MS symptomatology with neurovegetative depressive symptoms such as fatigue, sleeping problems and cognitive impairment, estimated depression prevalence in MS might be overrated. It also remains unclear to what degree depressive symptoms are a neurological consequence of the disease or a psychological reaction to the presence of a chronic medical condition with an uncertain and unpredictable course [4]. Some studies that compared depression in MS with other neurologic conditions and chronic diseases, suggest that depression in MS can be partly attributed to the additional neurological impact of MS [4]–[6].

Irrespective of its unclear etiology, depression in MS patients causes significant suffering and disability. Depression is associated with fatigue, cognitive impairment, and poorer social support [7]. Moreover, it is related to lower quality of life [8], increased risk of suicide [9] and may adversely affect health status via effects on the immune system or indirectly by influencing behavior that affects risk of MS exacerbation [10],[11].

However, depression in MS patients often stays undiagnosed [12]. There may be several explanations for the high level of unrecognized depression in MS patients. It is suggested that MS patients are not actively screened and diagnosed by their clinician on depression. In addition, patients could feel resistance to disclose their emotional problems or perceive them as an unsolvable component of the disease, therefore leaving them unmentioned [3]. Besides, as a result of overlapping symptomatology, confounded symptoms may be entirely attributed to MS when in fact a portion of those symptoms are attributable to depression. However, depression does not seem to remit spontaneously and may even worsen over time if not treated [11].

MS patients seem to respond well to psychotherapeutic and/or medical treatment for depression [13],[14]. Depression in MS patients seems to be related to poor problem solving skills [7], and learning various coping strategies has been found to reduce symptoms of depression in MS patients [14]. Research shows that Cognitive Behaviour Therapy (CBT) with a focus on developing sufficient coping skills is preferred to insight-oriented or supportive group therapy [11],[14],[15]. Problem Solving Therapy (PST) is a form of CBT and assumes that depressive symptoms can be caused by (practical) problems people face in their daily lives combined with poor problem-solving skills. PST focuses on enabling people to solve problems by teaching them more adequate problem-solving skills and helping to accept those problems that cannot be changed [16],[17]. PST in particular seems a favourable treatment for people with depressive symptoms and a somatic disease [18]. Nevertheless, the literature on PST for depression in MS patients is limited [19].

Given the evidence for its responsiveness to treatment, it is remarkable that depression in MS patients is so infrequently treated [3],[13]. Apart from general obstacles as lack of time, no self-perceived need for care or stigma associated with treatment, MS patients may have disease-related barriers such as transportation problems, physical immobility, fatigue and exacerbations of the disease that might interfere with having face-to-face treatment [14]. Consequently, medication consults or face-to-face psychotherapy may not be feasible forms of treatment for some MS patients [20]. Therefore, alternative treatment delivery should be considered to increase access to mental health care. Telephone administered CBT has previously shown to be more effective in reducing depressive symptoms in MS patients compared to MS patients receiving supportive emotion-focused therapy [21] or no mental healthcare at all [22]. Recently, the Internet has grown as an important tool for delivering mental health interventions [23]; Internet-based CBT or PST appear to be as effective as face-to-face therapy [24] and a successful method of treatment for depression in general [24],[25]. Internet-based treatment is easily accessible, cost-effective and can reach a large number of people with functional impairments due to physical health problems which makes it an attractive treatment for the MS population.

However, there are few publications on Internet-based treatment for depressed MS patients. Recently, a multicenter trial was suggested, based on a pilot study that explored Internet-based CBT for the treatment of depression [26]. Qualitative data from this research group showed that existing Internet-based CBT packages might not just be appropriate for MS patients due to MS related physical and cognitive impairments, inappropriate content, social isolation and problems with computer use [27]. However, data from our recent pilot study on Internet-based treatment for depression in MS showed evidence that Internet-based self-help PST treatment [28], adjusted to MS patients, can be a feasible treatment [29]. Patients reported satisfaction with the intervention which reduced depressive symptoms, especially in those MS patients who completed the intervention. These findings encourage us to examine the effectiveness of this Internet-based self-help course for treatment of depressive symptoms in MS in a randomized controlled trial (RCT) with longer follow-up. With an easily accessible Internet-based self-help intervention we hope to improve the level of care and treat a group of MS patients with depressive symptoms who could experience disease-related barriers to participate in face-to-face counselling.

Unfortunately, dropout percentages from Internet-based interventions can be high and do not get enough attention [30]. Also in our pilot study, almost half of the patients did not complete the intervention. Ways to increase compliance rates should therefore be considered. However, specific components that are critical in improving compliance are difficult to identify and experimental manipulation of factors likely to increase compliance in e-health trials are scarce [31]. A meta-analysis suggests that use of mobile phones and text-messaging could improve healthcare outcomes and the processes of care [32] and a RCT showed that telephone reminders increased the frequency of visits to the site of a self-help Internet program for depressive symptoms compared to no reminders [33]. Recently, Mohr and colleges [34] investigated the feasibility of a multimodal e-mental health treatment for depressed patients' in a pilot study, and suggested that joint effects of Internet and telephone administered support for depression are promising. In order to further increase compliance, we therefore plan to use telephone support in

the form of text-messages in addition to the Internet-based intervention. However, whether extra text-messages would enhance compliance rates for Internet-based PST is not known.

The aims of our RCT will therefore be multiple. First, we will examine the effectiveness of an Internet-based PST self-help intervention on the primary outcome measure depressive symptoms in MS patients and on secondary outcome measures related to depression and MS such as quality of life, fatigue and cognitive functioning. If the intervention shows to be effective, predictors of a favorable outcome will be further explored. Finally, we will investigate whether text-messages added to the intervention will be effective to increase compliance rate of Internet-based treatment.

METHODS

Study design

The presented study is a RCT in which a 5-week Internet-based self-help PST intervention will be tested versus a waiting list control group. Eligible and consenting patients will be assessed at baseline (T0), within a week after the intervention (T1), at four months (T2) and at ten months follow-up (T3: only the intervention group). The control group will be measured at the same moments in time. Patients in the waiting list condition who still want to participate in the intervention after they completed the four months follow-up assessment are again measured after the intervention (T4), four months later (T5) and at ten months follow-up (T6). Data will be collected by self-report measures administered through the Internet. In addition, a telephone interview at baseline will be carried out by trained research staff.

Randomization takes place at individual level after baseline measurements (T0). We will use block-randomization with variable block sizes. A randomly allocated number of patients who take part in the intervention will receive supportive text-messages on their mobile phones in addition to the intervention. Allocation will be unknown to the investigators and will be performed by an independent researcher using a computerized random digit generator. The study protocol was approved by the Medical Ethics Committee of the VU University Medical Center (VUmc) (registration number 11/047). Written informed consent is obtained from all participants. Figure 6.1 displays the flowchart of the study design.

Recruitment

MS patients will be recruited from the Neurology Department of the VUmc, through calls in MS newsletters and Internet-sites concerning MS (e.g. Dutch MS cooperation, MS Centres), at MS meetings and via MS nurses. Interested patients will be asked to complete an online screening on their depressive symptoms, and several socio-demographic and MS-specific questions (i.e. year of diagnosis, onset of first symptoms, medication usage, type of MS). Eligible patients will be further informed about the study and asked to return written informed consent. Subsequently, patients general practitioner (GP) and neurologist will be informed about participation.

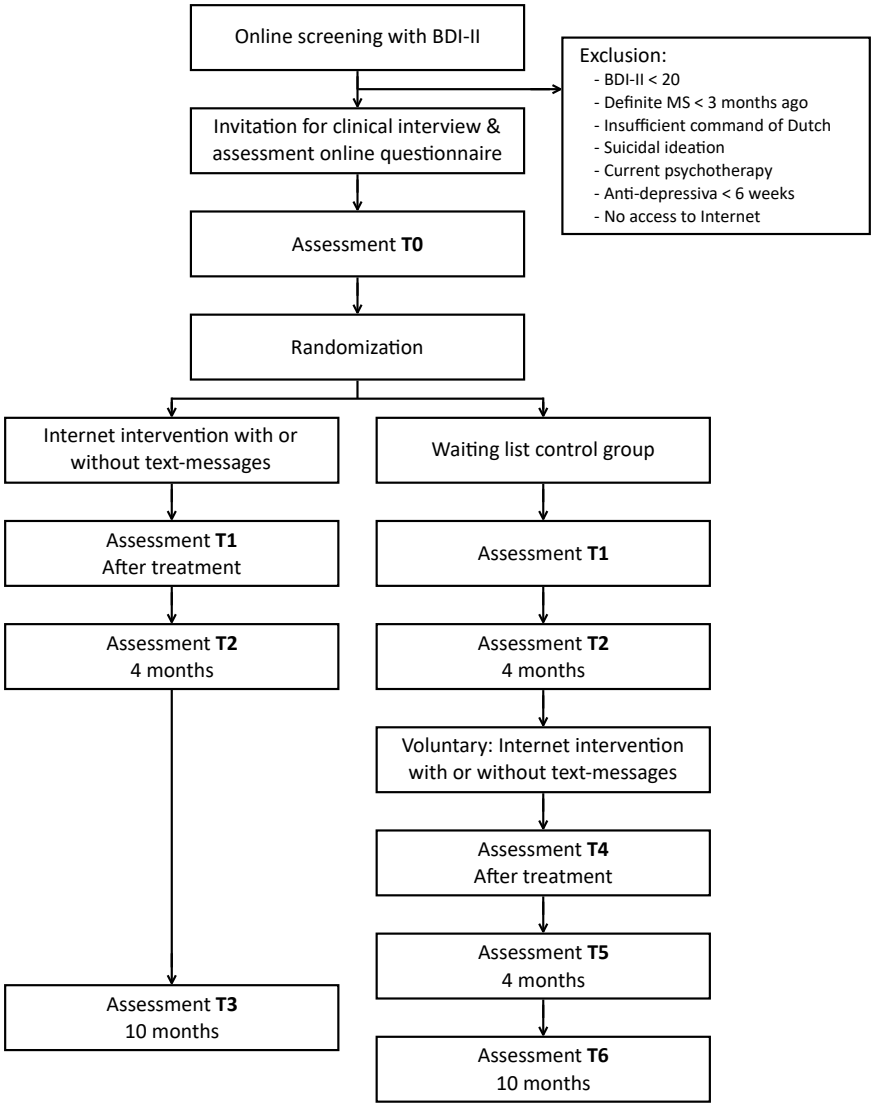

Figure 6.1 Flowchart of the study design.

Inclusion and exclusion criteria

MS patients with depressive symptoms who are willing to take part in an Internet-based self-help course can participate in the study. Patients (i) have to be 18 years or older, (ii) score 20 or higher on the Beck Depression Inventory (BDI-II) [35], indicating a moderate or severe depression and (iii) report a diagnosis of definite MS more than 3 months ago which will also be confirmed by their neurologist. Potential patients will be excluded if they are currently receiving psychotherapy, do not have Internet access, do not have a sufficient command of the Dutch language, or report suicidal ideation. Patients will not be excluded if they are taking prescribed medication for depression or anxiety disorders over 6 weeks with stable dosage.

To exclude patients with suicidal intention, item 9 'Suicidal thoughts or wishes' of the BDI-II will be used. Patients who score '3' ("I would kill myself if I had the chance"), will be contacted, further assessed and excluded and referred to their GP if necessary. Suicidal ideation will be also checked with an interviewer-rated scale of current suicidal ideation of the WHO-Composite International Diagnostic Interview (CIDI, World Health Organiszation (WHO) version 2.1) [36]. Patients with a score of 29 or higher on the BDI-II will be monitored extra.

Interview

A clinical diagnosis of Major Depression Disorder and/or Anxiety Disorder according to DSM-IV-TR criteria will be established by a standard telephonic interview using the WHO CIDI [36]. Neurological and medical conditions can create difficulties in assessing depression by a structured measurement as the CIDI. The CIDI asks patients how much of their sadness and anhedonia is a result of their medical illness or medications. In case patients indicate that their depressive symptoms are due to these attributes, a psychiatric diagnosis is not given. We decided that in case MS patients reported their MS or MS medication to be the reason for their sadness or anhedonia, the interviewer makes a note and scores the item negatively.

Further, the Perceived Need of Care Questionnaire (PNCQ) [37] will be used to measure patients' utilization of health care resources, needs for mental health care and the meeting of those needs. Further, the telephonic version of the Expanded Disability Status Scale [38] will be used to asses physical (MS) functioning and disability level.

Outcome measures

Primary outcome measure

The primary outcome is the change in depressive symptoms defined by a change in the sum score on the Beck Depression Inventory (BDI-II, second edition) [35],[39]. This self-report instrument is most often used to measure depression severity in MS patients [3], and has shown to be valid, reliable and appropriate for the MS population [40],[41].

Secondary outcome measures

Secondary outcomes will include measures of anxiety, fatigue, cognitive functioning, physical and psychological impact of MS, quality of life, problem solving skills, social support, mastery,

satisfaction and compliance rate. The measurement scales mentioned below have shown to be reliable, valid and responsive, and are widely used as an outcome measure in MS research and/or research on psychiatric conditions.

Anxiety will be assessed with the Beck Anxiety Inventory [42] and the subscale of the Hospital Anxiety and Depression Scale [43]. We will use the Fatigue Severity Scale (FSS) [44] and Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) [45] to measure fatigue and cognitive functioning, respectively. In addition, we will use the Multiple Sclerosis Impact Scale (MSIS-29) [46] to assess the physical and psychological impact of MS and the EuroQol quality of life measure comprising a five-part questionnaire (EQ-5D) and a visual analogue self-rating scale (EQ-VAS) [47]. Social support will be measured with the Social Support Inventory [48] which contains questions on details about social support from the four most intimate persons. We will use the Social Problem Solving Inventory-Revised (SPSI-R) to determine individual problem-solving skills [49]. Furthermore, Mastery or locus of control, is measured by an abbreviated version of the Pearlin Mastery Scale [50]. Between follow-ups, psychotherapy and -medication usage will be registered.

With the Client Satisfaction Questionnaire (CSQ-8) [51] we will check whether patients were satisfied with the care they received. The Visual Analogue Scale (VAS) will be assessed to evaluate patients opinions about the intervention as a whole, the website and received support, (via the website and by text-messages if applicable) and additionally explore reasons for drop-out. Feasibility of additional text-messages will further be assessed by compliance rate; data on number of treatment sessions and drop-out will be collected. Table 6.1 describes the measures used at each assessment point.

Internet-based problem solving treatment

The Internet-based self-help intervention examined in this study is an online problem solving therapy (PST) [16]. We adjusted the original online intervention [28] for MS patients with co-morbid depression, conserving the intent of the PST-based intervention. Modifications concerned additional information about MS and its psychosocial consequences and texts and examples applying to MS patients. We also added a mood-chart to the intervention for daily mood-registration during the course. The mood-chart could stimulate patients to visit the website regularly and therefore enhance compliance. In addition, it offers the possibility to monitor the patients mood. The whole intervention exists of five modules with text, exercises and figures, and is called 'Worry Less' ("Minder Zorgen"). Patients are asked to attend one module a week and work on their assignments for at least 2 hours per week.

Patients can access the intervention from their personal computers via the Internet (https://minderzorgen.e-behandeling.nl). Support during the intervention will be provided by trained psychologists and supervised clinical psychology Master students, and consists of communication through brief, weekly e-mails sent through the website and a weekly standardized e-mail to announce a new module. The e-mail correspondence is merely intended to facilitate the patient's effective use of the self-help method. Patients have the possibility to contact their coach at any moment for additional support via the website.

Table 6.1 Summary of measures.

Measure	T0: Baseline	T1: post-treatment	T2: 4-months Follow-up	T3: 10-months Follow-up
Interview				
Composite International Diagnostic Interview (CIDI)	X			
Perceived Need of Care Questionnaire (PNCQ)	X			
Expanded Disability Status Scale (EDSS)	X			
Self-report measurements				
Demografics & Medical MS data	X			
Medication and treatment information	X	X	X	X
Beck Depression Inventory (BDI-II)	X	X	X	X
Beck Anxiety Inventory (BAI)	X	X	X	X
Hospital Anxiety and Depression Scale (HADS-A)	X	X	X	X
Fatigue Severity Scale (FSS)	X	X	X	X
Multiple Sclerosis Neuropsychological Questionnaire (MSNQ)	X	X	X	X
Multiple Sclerosis Impact Scale (MSIS-29)	X	X	X	X
EuroQol (EQ-6D)	X	X	X	X
Social Support Inventory	X	X	X	X
Social Problem Solving Inventroy-Revised (SPSI-R)	X	X	X	X
Pearlin Mastery Scale	X	X	X	X
Client Staisfaction Questionnaire (CSQ-8)		X		X
Visual Analoge Scale (VAS) to evaluate the intervention		X		

Text-messages

As part of the intervention, a number of patients will receive weekly text-messages on their mobile phones to support them during the intervention with the aim to enhance compliance. Patients will be randomly assigned to the intervention with- or without text-messages. In the latest case, patients will receive four standard text-messages a week. Text-messages will be sent to their mobile phones 1) at the start of a new module, 2) during the week to remind patients to fill in the exercise and mood-chart, 3) when homework is handed in by email, and 4) when feedback is returned by their coach. When homework is not handed in on time, patients will receive a reminder text-message. Patients cannot reply to the text-messages.

Waiting list control group

Patients randomized to the waiting list control group receive no Internet-based PST. In accordance with the procedure of patients who participate in the intervention, patients in the waiting list control group are free to accept any medical or psychological intervention given in the time period of the study. The received mental healthcare will be registered. After completion of the four months follow-up assessment, patients are offered to participate in the Internet-based intervention on voluntary basis irrespective their BDI-II score at T2. Patients who subsequently take part in the intervention and follow-up measurements will be additionally analysed.

Sample size

The power calculation is based at the comparison at T1 to T0 between the two groups. We want to be able to demonstrate moderate effects (d=0.5) on the primary outcome measure, while using a power 0.80, with alpha set at .05 (two-tailed). Therefore, a total set of n=64 completers is needed in each condition. Taking into account the drop-out percentage of our pilot, we aim to include 166 patients.

Analysis

Non-parametric and parametric statistical tests are used to assess differences between the conditions with regard to baseline assessment of all relevant demographic and clinical variables. Missing data will be processed using regression imputation or a conservative Last Observation Carried Forward method (LOCF) (depending on the sort and size of the missing data). Analysis will be based on the intention-to-treat principle. Paired t-tests are used to assess the changes within each condition between pre-treatment and post-treatment. Difference in outcome between the Internet-based intervention and waiting list control group is evaluated by means of mixed model analysis of covariance and baseline differences will be included as a covariate in the analyses. Treatment effect over time will be tested by adding a group*time interaction term into the model. Cohen's formula will be used to evaluate the magnitude of the effect of the intervention on outcome measures [52]. To calculate clinically significant improvement and recovery we will use the standardized method of Jacobson and Truax [53]. If the intervention shows to be effective, predictors of outcome will be explored by analyses of interaction between patients characteristics and treatment. Data of waiting list patients who decided to participate in the intervention will be analysed separately. Finally, descriptive statistics of compliance rate and satisfaction will be used to explore the feasibility of text-messages as a way to increase compliance rate to Internet-based treatment.

DISCUSSION

The described study protocol is designed to investigate the effectiveness of an Internet-based self-help PST intervention for depressive symptoms in MS patients in a RCT. Treatment through Internet offers the possibility to reach a group of underserved MS patients who could experience disease-related barriers to participate in face-to-face counselling. Besides, the self-help aspect of

Internet-based treatment could be appealing to a group of patients that already is dependent of professionals in the medical circuit because of their MS. According to our knowledge, the effectiveness of Internet-based treatment for depressive symptoms in MS patients has not been examined yet. Our trial will also shed more light on the applicability of PST in itself for patients who suffer from MS.

In order to conduct a high-quality trial, a multidisciplinary team with various expertises related to MS and depression was involved in the development of the intervention and the study design. Ways to prevent early termination during the intervention were carefully taken into account since high drop-out percentages in e-health interventions are a common phenomenon. Although multimodal e-mental health treatment seems a promising candidate to increase compliance, additional research on this subject is needed [34]. Evaluation of the effectiveness of text-messages in addition to Internet-based treatment seems therefore a valuable aspect of our trial. Nevertheless, it is still unclear whether effectiveness of additional text-messages can be determined as the trial is powered to demonstrate effects of the intervention and not of text-messaging. Further, follow-up assessments to explore Internet-based PST effects on the long-term could be considered another strength of our trial since data on enduring treatment effects for depression in MS are often not available [11].

The external validity of our study is high because of the low level of exclusion criteria and the use of Internet that enables us to reach and treat a large part of the MS population. It should be noted that Internet-based treatment may not be suitable for MS patients who are not familiar with the Internet, or who suffer from MS related problems such as impaired vision and arm/hand dysfunction. In addition, we will exclude patients with mild depressive complaints (BDI-II<20). As a consequence, evidence will be lacking whether the intervention could be effective for this group of patients. However, our pilot-study [29] showed that patient with more severe depressive symptoms experienced more benefit from the intervention than patients with fewer depressive complaints. Moreover, patients with fewer depressive symptoms at baseline (<20) were more likely to drop out of treatment and indicated to be less satisfied with the intervention. A meta-analysis [23] supports this finding and suggests that patients with less severe psychological difficulties may be less motivated to receive ongoing help. Driessen and colleagues concluded in their meta-analysis [54] that psychological treatment might even be more efficacious for more severely depressed patients than low severely depressed patients. For these reasons we decided to focus on MS patients with moderate or high depressive complaints.

To conclude, a study protocol to investigate the effectiveness of Internet-based PST for depressive symptoms in MS patients is presented in order to enhance methodological clarity and further research on treatment for depressed MS patients. Internet-based PST offers the possibility to reach and treat many MS patients with depressive symptoms and to improve the quality of care. Our RCT is aimed at contributing to better recognition and adequate treatment of depressive symptoms in MS patients in the future.

Acknowledgements

This work was supported by Stichting MS Research (grant number 09-678 MS).

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7

INTERNET-BASED TREATMENT FOR DEPRESSION IN MULTIPLE SCLEROSIS: A RANDOMIZED CONTROLLED TRIAL

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Multiple Sclerosis Journal. 2016; [Epub ahead of print].

ABSTRACT

Background: Depression in multiple sclerosis (MS) patients is common but may stay untreated. Physical limitations impede face-to-face treatment. Internet-based treatment is therefore a promising tool for treating depression in MS.

Objectives: To investigate effectiveness of a guided Internet-based problem-solving treatment (IPST) for depressed MS patients.

Methods: MS patients with moderate or severe depressive symptoms were randomly assigned to IPST or a wait list control. Primary outcome was the change in depressive symptoms defined by a change in sum score on the Beck Depression Inventory Second Edition (BDI-II). Assessments took place at baseline (T0), within a week after the intervention (T1), and at 4 months follow-up (T2). Analyses were based on the intention-to-treat principle.

Results: A total of 171 patients were randomized to IPST (*n*=85) or a wait list control (*n*=86). T1 was completed by 152 (89%), and T2 by 131 patients (77%). The IPST group and wait list control showed large significant improvements in depressive symptoms, but no differences were found between groups at T1 (*d*=0.23, 95% confidence interval (CI)=-0.17–0.63, *p*=.259) and T2 (*d*=0.01, 95%CI=-0.44–0.46, *p*=.953).

Conclusions: We found no indication that IPST for MS patients with moderate or severe depression is effective in reducing depressive symptoms compared to a waiting list. Large improvements in the wait list control were unexpected and are discussed.

INTRODUCTION

Depression in MS is common (24%) [1] and has a large impact on quality of life. It is related to fatigue, cognitive dysfunction, working problems and disrupted social support and family systems and may adversely affect health outcome [2],[3]. Cognitive behavioral therapy (CBT) is an effective treatment for depressed patients with medical conditions including MS [4],[5]. Still, many MS patients remain untreated [3]. Under-treatment may be due to disease-related barriers such as transportation difficulties, physical immobility, fatigue and MS exacerbations that impede face-to-face treatment [6].

Guided Internet-based cognitive behavioral therapy (ICBT) is considered a good alternative for face-to-face treatment [7],[8]. ICBT is easily available, cost-effective, and can reach a large number of people with functional impairments due to physical health problems. Internet-based interventions demonstrated psychosocial benefits in chronic illness settings, [9] and research of telemedicine technologies in treating depression in (housebound) MS patients was recently advised in MS guidelines [3]. Although this patient group may likely benefit from ICBT, there are still few publications on ICBT for depressed MS patients, [10]–[12] and the results are encouraging. In an uncontrolled pilot study, we found that Internet-based problem-solving treatment (IPST), CBT with a focus on developing sufficient coping skills, is a feasible treatment for depression in MS, and may reduce depressive symptoms [10].

Here, we present a randomized controlled trial (RCT) to investigate the effectiveness of guided IPST for depression in MS [13]. We aimed to examine effectiveness of IPST on the primary outcome measure depressive symptoms and on secondary outcome measures related to depression in MS such as anxiety, quality of life, fatigue, cognitive and physical functioning.

PATIENTS AND METHODS

Trial design

A two-armed RCT in which an Internet-based guided self-help problem-solving treatment (IPST) was compared with a wait list control. An extensive description of the study protocol can be found elsewhere [13]. The trial was approved by the Medical Ethics Committee of the VU University Medical Center and registered with the Dutch Trial Registry (NTR2772).

Patients

MS patients were recruited at several MS centres throughout the Netherlands, and through calls in MS newsletters and Internet sites, and were invited to complete an online screening assessment. Patients (18 years or older) with sufficient command of Dutch language and Internet access were eligible to participate if they had a) a diagnosis of MS (>3 months) and b) a score of 20 or more on the Beck Depression Inventory Second Edition (BDI-II), indicating moderate or severe depression. Patients taking prescribed psychotropic medication for more than 6 weeks with stable dosage were allowed to participate. Those receiving psychotherapy or with an elevated risk for suicide

assessed with item 9 of the BDI-II and an additional telephone interview, were excluded. All patients gave written informed consent.

IPST

The guided self-help intervention "Minder Zorgen" ("Worry Less") was an existing and tested IPST that was adjusted for MS patients [13]. The intervention consisted of five sequential modules with text, examples and assignments that patients could access from their personal computers via the Internet. Patients were advised to complete one module per week but could extend the intervention period up to 10 weeks if extra time was needed. Support during the intervention was provided by trained psychologists and supervised psychology master students and consisted of weekly emails. Patients could contact their coach at any moment for additional support via the website. Support was directed to help the patient work through the intervention.

Patients randomized to the wait list control received no IPST. After completion of the 4 months follow-up assessment, they were offered the possibility to participate in the intervention.

Outcomes

Eligible and consenting patients were assessed at baseline (T0), within a week after the intervention (5–10 weeks) (T1), and at four months follow-up (T2). The wait list control was measured at the same moments in time. Data were collected by self-report measures administered through the Internet, and a telephone interview at baseline by trained research staff.

The primary outcome was the change in depressive symptoms defined by a change in sum score on the BDI-II. Post-hoc analyses for BDI-II subscale scores [14], and for moderate (BDI-II=20–28) and severely (BDI-II≥29) depressed patients at baseline were additionally performed (supplementary material). Secondary outcome measures were the anxiety subscale of the Hospital Anxiety and Depression Scale, Beck Anxiety Inventory, Fatigue Severity Scale, Multiple Sclerosis Neuropsychological Questionnaire, Multiple Sclerosis Impact Scale, EuroQol quality of life measure, subscales of the Social Problem Solving Inventory-Revised, and the abbreviated version of the Pearlin Mastery Scale.

At baseline, a clinical diagnosis of a Depression Disorder and/or Anxiety Disorder according to Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition, Text Revision; DSM-IV-TR) criteria was established by a standard telephone interview using the Composite International Diagnostic Interview. The telephone version of the Expanded Disability Status Scale was used to assess physical (MS) functioning and disability level. Other additional baseline measures concerned socio-demographic and MS-specific questions. Patients' neurologists gave written confirmation of the MS diagnosis. Finally, the use of psychotherapy and/or psychotropic medication since baseline assessment was registered, and satisfaction of received care and text-messages (if applicable) was measured with the Client Satisfaction Questionnaire (CSQ) and evaluative questions using Visual Analogue Scales (VAS). Adverse events were assessed post-hoc by deterioration (increase of significant depression severity; exceeding the lower threshold for suicidal ideation: score>1 on BDI-II item 9) and non-response (no clinically significant change or deterioration) [11],[15]. More extensive information can be found in the protocol [13].

Sample size

The power calculation was based on the comparison of T1 to T0 between the two groups. To demonstrate moderate effects (Cohen's *d*=0.5) on the primary outcome measure (depressive symptoms), while using a power 0.80, with alpha set at 0.05 (two-tailed), a total set of *n*=64 patients was needed in each condition. Taking into account an anticipated dropout percentage (about 25%), at least 166 patients had to be included to certify sufficient power [13].

Randomization and Blinding

Patients were randomized by an independent researcher after baseline, using a blocked randomization scheme. A randomly allocated number of patients who took part in the intervention received four weekly supportive text messages on their mobile phones aimed to enhance treatment adherence. Text messages were in addition to email support that was received by every patient in the IPST group. Patients were informed about their assignment by the first author (R.E.B). Due to the nature of the intervention neither patients nor providers of support could be blinded for the intervention. Randomization and statistical analysis were performed blindly.

Statistical analyses

Analyses were based on the intention-to-treat principle. *T*-tests and chi-square tests were used to investigate baseline differences in demographic and clinical variables between both arms. Linear mixed-model (LMM) analyses were conducted through a marginal model to evaluate the difference in depressive symptoms (primary outcome) and secondary outcomes between the IPST group and wait list control. LMM analysis is able to handle missing data due to dropout under the assumption that missing data are Missing At Random [16]. We used an LMM analysis due to progressive insight and deviated from the statistical method described in our protocol (last observation carried forward method and regression imputation). Further, a subgroup analysis was performed using the same procedure as in the intention-to-treat analyses with patients who fulfilled criteria for treatment adherence (at least 3 modules completed). Cohen's [17] formula was used to calculate effect sizes for the estimated differences [18]. The standardized method of Jacobson and Truax (1991) [19] was used to determine clinically significant improvement, deterioration, and recovery. Recovery was defined as reliable change plus a score of 13 or lower on the BDI-II [14]. Finally, descriptive statistics and a chi-square test were used to explore the feasibility of text-messages as a way to increase compliance to the intervention. Data were analyzed using IBM SPSS statistics version 20.0 (IBM SPSS Statistics for Windows, Armonk, NY, USA).

RESULTS

Patients

From July 2011 to August 2015, 495 MS patients were assessed for eligibility, of whom 171 were randomized to IPST (*n*=85) or wait list control (*n*=86) (Figure 7.1). In all, 19 patients (11%) did not complete T1 – 11 patients in the IPST group and 8 patients in the wait list control. At T2

another *n*=21 (12%) patients dropped out, leaving *n*=64 (75%) patients in the IPST group and *n*=67 (78%) in the wait list control. Dropout rates were not differential with respect to IPST versus wait list control at T1 (*p*=.449) and T2 (*p*=.687). Average time of T1 was 9 weeks (IPST; 9.1±2.6/ wait list control; 9.2±2.5). Baseline demographics and clinical characteristics were much the same between the IPST group and wait list control, and are displayed in Table 7.1.

Differences in baseline characteristics were assessed for patients who completed T1 and those who did not. Non-completers had a higher mean BDI-II score (30.6±7.3 versus 27.3±6.3, *p*=.035), and were more often taking anti-depressant medication (16% versus 13%, *p*=.032).

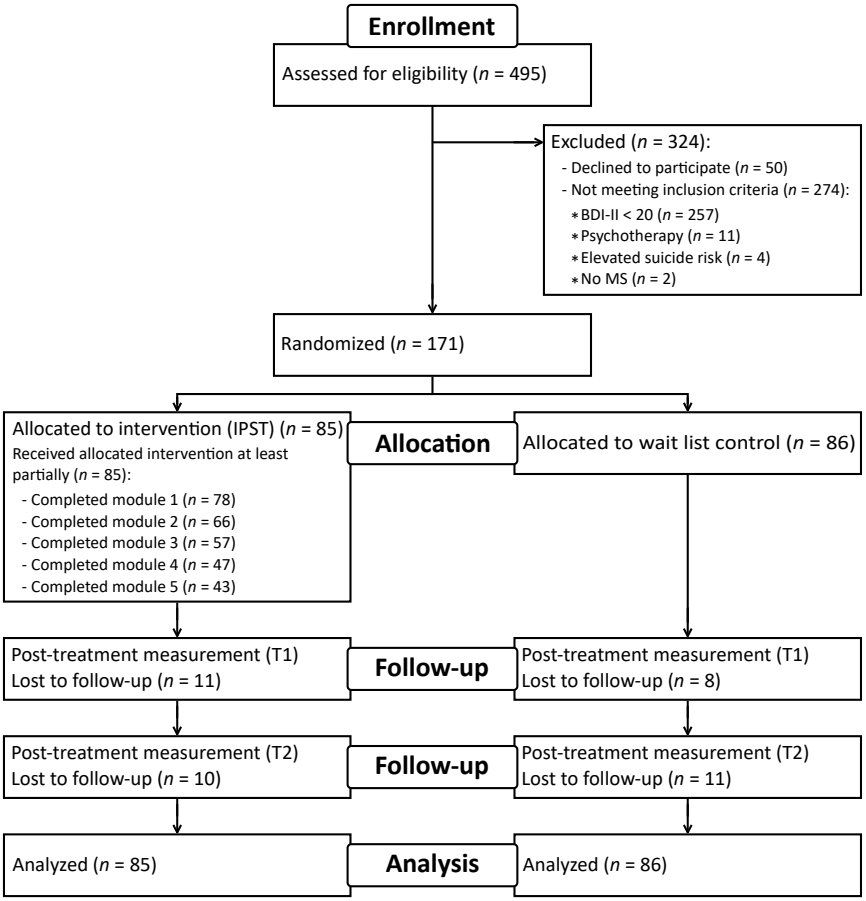

Figure 7.1 Flow Diagram.

Table 7.1 Baseline demographics and clinical characteristics.

	All patients (*n*=171)	**IPST (*n*=85)**	**Wait list control (*n*=86)**
	mean (SD) or %	**mean (SD) or %**	**mean (SD) or %**
Demographics			
Age, years	48.9 (10.5)	48.4 (11.1)	49.4 (9.9)
Gender, women	80.1	83.5	76.7
Country of birth			
Netherlands	93.6	94.1	93.0
Other	6.4	5.9	7.0
Education[a]			
Low	1.2	0.0	2.3
Middle	53.2	56.5	50.0
High	45.6	43.5	47.7
Marital Status			
Relationship, yes	78.4	72.9	83.7
MS characteristics			
Years since MS onset	11.2 (8.1)	11.1 (8.3)	11.3 (8.0)
Type of MS (by neurologist)			
Benigne	2.3	3.5	1.2
Relapsing Remitting	55.0	54.1	55.8
Secondary Progressive	28.1	25.9	30.2
Primary Progressive	9.9	9.4	10.5
Relapsing Progressive	3.5	4.7	2.3
Missing	1.2	2.4	0.0
EDSS (*n*=170)			
0–1.5	3.5	4.7	2.3
2–4	50.9	48.2	53.5
4.5–6	17.5	18.8	16.3
≥6.5	27.5	27.1	27.9
Medication			
MS disease modifying (*n*=152)	32.9	36.5	29.5
MS Symptom relief (*n*=152)	52.0	48.6	55.1
Antidepressants, yes	12.9	11.8	14.0
Diagnoses			
Depressive Disorder			
First episode (MDD)	58.5	53.4	63.3
Current depressive disorder	55.0	56.5	53.5

Table 7.1 Continued.

	All patients (*n*=171)	IPST (*n*=85)	Wait list control (*n*=86)
	mean (SD) or %	mean (SD) or %	mean (SD) or %
Major Depressive Disorder	52.0	50.6	53.5
Dysthemia	2.9	5.9	0.0
Life-time depressive disorder (MDD and/or Dysthemia)	71.3	72.9	69.8
Anxiety Disorder			
Current	31.8	30.6	32.9
Life-time	41.2	35.3	47.1
Comorbid depressive and anxiety disorder			
Current	20.1	18.8	21.4
Life-time	32.9	28.2	37.6
Symptom severity			
Depression (BDI-II)	27.7 (6.4)	28.2 (6.6)	27.3 (6.3)
Anxiety (HADS)	10.4 (3.2)	10.4 (3.2)	10.5 (3.2)

IPST = Internet-based Problem-Solving Treatment; MS = Multiple Sclerosis; EDSS = Expanded Disability Status Scale: 0–1,5 = no complaints, 2–4 = low-to-moderate complaints, 4–6 = moderate-to-severe complaints, ≥6,5 = very severe complaints; BDI-II = Beck Depression Inventory Second Edition; HADS = Hospital Anxiety and Depression Scale; SD = Standard Deviation.

[a] Low: primary education, Middle: lower general secondary education, intermediate vocational education or high school, High: higher vocational education or university.

Adherence

A total of 57 out of 85 patients (67%) completed at least three modules and were considered treatment completers (mean number of modules for treatment completers was 4.58±0.78 versus 1.07±0.77 for non-completers). Treatment completers had a lower mean age than non-completers (46.2±10.4 versus 52.9±11.3, p=.008), but did not differ in gender, education level, disability level and depression severity at baseline. Main reasons for drop-out were computer related problems (*n*=5/28), lack of time (*n*=7/28), the intervention not meeting patients' needs/ starting other treatment (*n*=11/28), MS-related problems such as pain, vision problems or hospitalization (*n*=5/28).

In total, 40 patients in the IPST arm were allocated to receive additional text messages. Four patients refused these text messages (unfamiliar with/no mobile phone (*n*=2), or not useful (*n*=2)). Additional text-messages did not increase the compliance rate of the intervention (three or more modules completed), compared with no text messages (65% versus 69%, p=.703).

Health care use

From baseline to T1 there was no difference in healthcare use between the IPST and wait list control: 18% versus 13% contacted a psychologist or psychiatrist (p=.414), and 15% versus 17% used anti-depressants (p=.258).

Effects

Improvement on outcome measures

Results of the intention-to-treat analyses are displayed in Table 7.2 and 7.3. A high within-group effect size was found for the primary outcome of depressive symptoms for IPST (d=1.18, 95% confidence interval (CI)=0.88–1.47) and wait list control (d=0.95, 95%CI=0.67–1.23) at T1, and for IPST (d=1.11, 95%CI=0.78–1.43) and wait list control (d=1.12, 95%CI=0.80–1.44) at T2. No significant difference between groups was found at T1 (d=0.23, 95%CI=-0.17–0.63, p=.259) or at T2 (d=0.01, 95%CI=-0.44–0.46, p=.953) (Figure 7.2). Also no significant difference was found when comparing IPST completers (n=57, greater than or equal to three modules) with the wait list control at T1 (d=0.33, 95%CI=-0.11–0.77, p=.136) or at T2 (d=0.05, 95%CI=-0.43–0.53, p=.828). BDI-II post-hoc analyses showed no significant differences between IPST and the wait list control at T1 and T2 in subscale scores, and for severely depressed patients versus moderate depressed patients (supplementary material).

For the secondary analyses there was a difference between the two groups at T2 for mastery (d=0.34, t(169)=-2.294, p=.023) in favour of the wait list control which should be interpreted, however, as a negligible finding due to multiple testing. No other significant differences were found between groups at different time points.

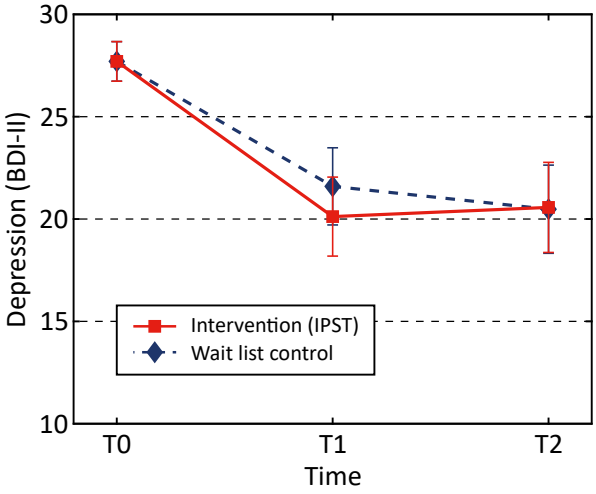

Figure 7.2 Depressive symptoms for the intervention group (IPST = Internet-based problem-solving treatment) and wait list control at baseline (T0), T1 (after the intervention) and T2 (4 months follow-up).

Clinical significant improvement and recovery

Based on the reliable change index (at least 5-points decrease on the BDI-II) [19], 66% (*n*=49/74) in the IPST group and 53% (*n*=41/78) in the wait list control showed a significant improvement in depressive symptoms at T1 (*p*=.087) and 63% (*n*=40/64) versus 60% (*n*=40/67) at T2 (*p*=.743). In the IPST group 24% (*n*=18/74) was recovered from depressive symptoms at T1 versus 18% (*n*=14/78) in the wait list control which did not differ significantly (*p*=.335). At T2, 28% of patients (*n*=18/64) was recovered in the IPST group versus 26% (*n*=17/67) in the wait list control (*p*=.722).

Satisfaction and Adverse events

In line with positive evaluations of other ICBT [8],[20], the majority of IPST patients (*n*=73) was satisfied (as measured with the CSQ) with the help they had received (89%) and would recommend this kind of treatment to others (71%). A total of 80% rated the quality of the intervention as good or excellent and the majority thought the intervention helped them to deal with their problems (66%). The website was rated with an average of 7.2±1.3 on a 10-point VAS and most patients indicated that the website was clear (74%) and easy to use (77%). The majority was satisfied with the frequency of the feedback (85%) and rated its quality as good or excellent (78%).

We found no evidence of adverse events as a consequence of IPST. Post hoc analyses showed no significant difference with regard to the proportion of patients reporting significant deterioration for IPST (*n*=7/74) compared with the wait list control at T1 (*n*=5/78, *p*=.486). The threshold for suicidal ideation was met by one patient in the IPST group and two patients in the wait list control. Non-response was not significantly different for IPST (34%, *n*=25/74) versus the wait list control (47%, *n*=37/78).

Table 7.2 Mean scores for primary and secondary outcomes for the IPST group at T0 (*n*=85), T1 (*n*=74) and T2 (*n*=64) and the wait list control at T0 (*n*=86), T1 (*n*=78) and T2 (*n*=67).

		IPST	Wait list control
		mean (SD)	mean (SD)
Primary outcome			
Depression (BDI-II)	T0	28.2 (6.3)	27.2 (6.6)
	T1	20.3 (8.8)	21.0 (9.1)
	T2	20.8 (10.4)	20.1 (9.2)
Secondary outcomes			
Anxiety (HADS-A)	T0	10.4 (3.2)	10.4 (3.2)
	T1	9.0 (3.8)	9.3 (3.8)
	T2	8.8 (3.8)	8.9 (3.8)
Anxiety (BAI)	T0	18.4 (8.8)	18.5 (0.9)
	T1	15.7 (9.0)	17.4 (11.1)
	T2	16.3 (10.1)	17.1 (11.0)

Table 7.2 Continued.

		IPST	Wait list control
		mean (SD)	mean (SD)
Fatigue (FSS)	T0	5.8 (1.0)	5.8 (0.9)
	T1	5.7 (0.9)	5.7 (0.9)
	T2	5.7 (1.0)	5.6 (1.1)
Cognitive functioning (MSNQ)	T0	30.6 (10.9)	31.0 (10.1)
	T1	28.7 (10.5)	29.7 (10.0)
	T2	28.0 (10.4)	29.2 (9.8)
Physical and psychological impact of MS (MSIS-29)	T0	89.8 (22.8)	87.6 (21.1)
	T1	82.9 (22.8)	82.6 (23.3)
	T2	84.6 (25.0)	82.6 (32.2)
Quality of life (EQ-5D)	T0	0.47 (.3)	0.51 (.3)
	T1	0.52 (.3)	0.58 (.3)
	T2	0.46 (.4)	0.57 (.3)
Quality of life (EQ-VAS)	T0	57.7 (17.8)	58.1 (17.8)
	T1	59.1 (17.9)	59.9 (17.4)
	T2	58.0 (19.5)	60.4 (18.2)
Problem solving skills (SPSI-R npo)	T0	19.2 (7.8)	19.4 (7.4)
	T1	15.7 (7.3)	16.8 (7.6)
	T2	17.5 (7.0)	17.1 (7.3)
Problem solving skills (SPSI-R ppo)	T0	9.4 (3.6)	9.4 (3.4)
	T1	10.1 (3.5)	9.6 (3.4)
	T2	9.5 (3.4)	10.3 (3.5)
Problem solving skills (SPSI-R av)	T0	10.6 (5.9)	11.1 (5.5)
	T1	8.8 (6.0)	10.3 (5.8)
	T2	10.2 (6.2)	10.1 (5.1)
Mastery (Pearlin Mastery Scale)	T0	13.1 (3.7)	13.1 (3.5)
	T1	13.6 (3.6)	13.4 (3.7)
	T2	12.6 (4.0)	14.1 (4.5)

IPST = Internet-based Problem-Solving Treatment; BDI-II = Beck Depression Inventory Second Edition; HADS-A = Hospital Anxiety and Depression Scale-Anxiety subscale; BAI = Beck Anxiety Inventory; FSS = Fatigue Severity Scale, the scale ranged from 1 (strongly disagree with the statement) to 5 (strongly agree with the statement) instead of 1 (strongly disagree with the statement) to 7 (strongly agree with the statement) and was therefore recoded (1=1, 2=2.5, 3=4, 4=5.5, 5=7); MSNQ = Multiple Sclerosis Neuropsychological Questionnaire; MSIS-29 = Multiple Sclerosis Impact Scale-29; EQ-5D = EuroQol quality of life measure; EQ-VAS = EuroQol quality of life measure Visual Analogue Scale; SPSI-R = Problem Solving Inventory-Revised; npo = negative problem orientation scale, ppo = positive problem orientation scale, av = avoidance scale; SD = Standard Deviation.

Table 7.3 Test statistics and effect sizes of the differences in primary and secondary outcomes between the IPST group and wait list control, from linear mixed model analyses.

		t	*p*-value	Effect-size (*d*)
Primary outcome				
Depression (BDI-II)	Condition * T1	-1.133	.259	0.23
	Condition * T2	0.060	.953	0.01
IPST completers (*n*=57)	Condition * T1	-1.501	.136	0.33
	Condition * T2	-0.218	.828	0.05
Secondary outcomes				
Anxiety (HADS-A)	Condition * T1	-0.743	.458	0.11
	Condition * T2	-0.298	.766	0.05
Anxiety (BAI)	Condition * T1	-1.654	.100	0.20
	Condition * T2	-0.260	.795	0.04
Fatigue (FSS)	Condition * T1	-0.976	.331	0.17
	Condition * T2	0.502	.617	0.12
Cognitive functioning (MSNQ)	Condition * T1	-0.611	.542	0.06
	Condition * T2	-0.358	.721	0.04
Physical and psychological impact of MS (MSIS-29)	Condition * T1	-0.360	.719	0.03
	Condition * T2	0.395	.694	0.00
Quality of life (EQ-5D)	Condition * T1	-0.932	.353	0.13
	Condition * T2	-1.686	.094	0.29
Qualty of life (EQ-VAS)	Condition * T1	-0.255	.799	0.04
	Condition * T2	-0.507	.613	0.09
Problem solving skills (SPSI-R npo)	Condition * T1	-1.132	.259	0.14
	Condition * T2	-0.159	.874	0.02
Problem solving skills (SPSI-R ppo)	Condition * T1	0.772	.441	0.10
	Condition * T2	0.251	.802	0.20
Problem solving skills (SPSI-R av)	Condition * T1	-1.385	.168	0.16
	Condition * T2	0.466	.642	0.06
Mastery (Pearlin Mastery Scale)	Condition * T1	0.670	.504	0.09
	Condition * T2	-2.294	.023	0.34

IPST = Internet-based Problem-Solving Treatment; BDI-II = Beck Depression Inventory Second Edition; HADS-A = Hospital Anxiety and Depression Scale-Anxiety subscale; BAI = Beck Anxiety Inventory; FSS = Fatigue Severity Scale, the scale ranged from 1 (strongly disagree with the statement) to 5 (strongly agree with the statement) instead of 1 (strongly disagree with the statement) to 7 (strongly agree with the statement) and was therefore recoded (1=1, 2=2.5, 3=4, 4=5.5, 5=7); MSNQ = Multiple Sclerosis Neuropsychological Questionnaire; MSIS-29 = Multiple Sclerosis Impact Scale-29; EQ-5D = EuroQol quality of life measure; EQ-VAS = EuroQol quality of life measure Visual Analogue Scale; SPSI-R = Problem Solving Inventory-Revised: npo = negative problem orientation scale, ppo = positive problem orientation scale, av = avoidance scale.

DISCUSSION

MS patients with moderate or severe depression treated with guided IPST showed a large decrease in depressive symptoms that sustained over 4 months follow-up. A similar improvement was observed in the wait list control. Therefore, we found no indication that IPST is more effective than a waiting list.

Our findings contrast the result of a study executed in Germany showing effectiveness of ICBT (Deprexis) for depression in MS [11]. Both interventions studied are based on the principles of CBT. "Minder Zorgen" consisted of five sequential modules of problem-solving therapy (PST) with guided email support, whereas the fully automated "Deprexis" offers 9-week access to 10 modules with other CBT techniques next to problem solving. However, within-group effect sizes found for both interventions were substantial (medium for "Deprexis", large for "Minder Zorgen"), suggesting explanations for different between-group findings should not be attributed to the intervention per se.

The considerable decrease in depressive symptoms in our wait list control was unexpected and does not correspond with findings from (I)CBT trials for depression in MS [5],[11], or with literature on ICBT for depression in general [8]. Our findings of significant improvement in both arms, including the wait list control, resembles outcomes of several studies comparing ICBT with a wait list control for depressed outpatients, employees, or patients in a community sample [21]–[24]. Our results were unexpected and various explanations can be suggested.

First, clarification of our findings is unlikely to be found in the chosen study design, as the use of wait list controls often results in largest trial effect sizes [25]. In addition, we performed a high-quality trial with independent randomization and intention to treat analyses. The large number of participating patients and low drop-out rates (11%) are a major strength of our study. Second, our tested intervention is considered sufficient; the decrease in depressive symptoms in the intervention group was as expected, and improvement and satisfaction rates correspond to similar studies and our pilot [10],[20]. However, participants had moderate or severe depressive symptoms, where most ICBT studies have focused on mild-to-moderate depression [8],[11],[20]. Although ICBT for more severely depressed is still a field to explore [8],[20], previous findings suggest more severely depressed could benefit as much from low-intensity interventions or ICBT as less severely depressed [10],[26],[27] which is also supported by our post hoc analysis. Third, decreased depressive symptoms could be MS-related, as the BDI may measure symptoms of the physical condition along with symptoms of depression. However, most of these symptoms are unlikely to change significantly over the course of a relatively short period, and the BDI is suggested to be an adequate measure for depression in MS [3],[28]. Also, post hoc analyses showed no difference in BDI-II subscale outcomes between groups over time. Fourth, another explanation for improvement in the wait list control might be recruitment of highly motivated patients (the majority of patients applied themselves) who are willing to address their complaints, resulting in improvement accordingly. Even a small degree of contact with a clinician (e.g. interview) seems to lead to better (treatment) outcomes [29]. Fifth, around 15% of patients in both arms received mental healthcare outside our trial which could have affected results. Outcomes

for completers receiving no other mental healthcare between baseline and T1 and T2, were therefore additionally compared. Large improvement in depressive symptoms in the IPST group and wait list control remained and no significant differences were observed (supplementary material). Finally, decreased depression symptomatology in the wait list control could be a result of regression to the mean as high scores are more likely to decrease. It may represent the natural course of depressive symptoms in MS patients. In the general population, half of depressed patients recovers within 3 months [30], which may also apply to the MS population stressing the importance to distinguish between adaptive (negative) emotions that improve over time, and persisting emotional disorders with a need for treatment in this patient group.

Altogether, instead of an effect of the intervention, results showed an effect over time in both arms which should probably not be attributed to the study design, depression severity and assessment, or additional care. We feel that the explanation should be sought in spontaneous recovery of a highly motivated subsample of patients. ICBT may be a helpful intervention for depressed MS patients, but it probably has no added value in a select group of motivated patients. As findings on ICBT for depression in MS are inconsistent, more research is advised.

Even though large effect sizes were found within the two arms, around 75% of patients were not recovered at T1 and T2. Non-recovery may be due to high depression severity at baseline [26],[30], to low-intensity treatment, or might have to do with the MS-related depression itself that is suggested to be static [31] and more difficult to treat [32]. If MS-related depression is a more complex persistent condition, it is unrealistic to expect recovery from a single intervention, and combined treatment options should be considered [33]. Since persistent residual depressive symptoms increase the risk of relapse and poor functional and psychosocial outcomes [34], it is essential to further identify and understand non-recovery of depressed MS patients and adjust treatment accordingly [26],[30].

There are several limitations of our study. First, although the clinical interview at baseline is a strength of our study, it was not performed at T1/T2. Consequently conclusions are based on self-reported depression that may be prone to bias. Second, adherence rates of our intervention were substantially lower compared with face-to-face treatments [20]. Our effort to increase treatment adherence by adding telephone support (text messages) did not lead to the desired effect. Low ICBT adherence rates are a serious point of concern [35]. However, treatment adherence for MS patients was comparable or better compared with other ICBT interventions [20],[23],[24], which is encouraging as lower rates could have been expected due to MS-related complaints interfering with treatment [12].

Further research is thus needed to understand determinants of (I)CBT response, adherence and (disease-related) characteristic of depressed MS patients who may benefit from it. Potential advantages of combining ICBT with face to face treatment should be investigated as well as combinations with other treatments (e.g. medication) [33].

Acknowledgements

The randomized controlled trial was supported by 'Stichting MS Reseach' (Grant number 09-678). We would like to acknowledge D Wong, MSc, (GGZinGeest/VU University Medical Center) for the data management.

We would like to thank several colleagues for recruiting patients: from The Netherlands: R. Hintzen (Rotterdam), E. van Munster ('s-Hertogenbosch), B. van Geel (Alkmaar), N. Kalkers (Amsterdam), E. Hoogervorst (Nieuwegein), A. Huele (Amsterdam), N. Rauwerda (Tiel), D. Mulder and E. Simmelink (Groningen); from Belgium: M. D'Hooghe (Melsbroek).

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Supplementary material 7.A.1 Mean scores for BDI-II subscales (affective, cognitive, somatic) for the IPST group at T0 (*n*=85), T1 (*n*=74) and T2 (*n*=64), and the wait list control at T0 (*n*=86), T1 (*n*=78) and T2 (*n*=67).

		IPST	Wait list control
		mean (SD)	**mean (SD)**
Affective			
	T0	5.7 (2.2)	5.6 (2.0)
	T1	4.0 (2.4)	4.3 (2.3)
	T2	4.2 (2.8)	4.2 (2.2)
Cognitive			
	T0	8.5 (3.6)	8.3 (3.3)
	T1	5.9 (3.5)	5.7 (3.5)
	T2	6.0 (4.4)	5.8 (3.8)
Somatic			
	T0	14.0 (3.2)	13.3 (3.1)
	T1	10.4 (4.8)	11.1 (4.9)
	T2	10.6 (5.0)	10.1 (4.4)

BDI-II = Beck Depression Inventory Second Edition; IPST = Internet-based Problem-Solving Treatment; SD = Standard Deviation.

Supplementary material 7.A.2 Test statistics of the differences in BDI-II subscale outcomes between the IPST group and wait list control, from linear mixed model analyses.

		t	*p*-value
Affective			
	Condition * T1	-0.849	.397
	Condition * T2	-0.020	.984
Cognitive			
	Condition * T1	-0.033	.974
	Condition * T2	-0.524	.601
Somatic			
	Condition * T1	-1.881	.062
	Condition * T2	-0.231	.818

BDI-II = Beck Depression Inventory Second Edition; IPST = Internet-based Problem-Solving Treatment.

Supplementary material 7.B.1 Mean BDI-II scores for the IPST group and the wait list control with moderate or severe depressive symptoms at baseline at T0, T1 and T2.

		IPST		Wait list control	
		n	**mean (SD)**	**n**	**mean (SD)**
Primary outcome					
Moderate depressive symptoms (BDI-II)	T0	48	23.4 (2.5)	54	23.2 (2.8)
	T1	43	18.4 (9.0)	51	18.3 (7.6)
	T2	35	18.9 (11.3)	44	16.8 (7.2)
Severe depressive symptoms (BDI-II)	T0	37	34.3 (4.8)	32	34.1 (4.1)
	T1	31	22.8 (8.1)	27	26.2 (9.6)
	T2	29	23.1 (9.0)	23	26.3 (9.5)

BDI-II = Beck Depression Inventory Second Editon; IPST = Internet-based Problem-Solving Treatment; SD = Standard Deviation.

Supplementary material 7.B.2 Test statistics of the differences in primary outcome between the IPST group and wait list control for severe depressive symptoms versus moderate depressive symptoms at baseline, from linear mixed model analyses.

		t	***p*-value**
Primary outcome			
Moderate/Severe depression (BDI-II)	Severity * Condition * T1	-1.324	.187
	Severity * Condition * T2	-1.206	.230

BDI-II = Beck Depression Inventory Second Edition; IPST = Internet-based Problem Solving Treatment.

Supplementary material 7.C Differences in depressive symptoms for completers in the IPST group and wait list control receiving no other mental healthcare between baseline and T1 (*n*=129) and T2 (*n*=97), from regression analyses.

		B	**t**	***p*-value**
Primary outcome				
Depression (BDI-II)	T1	-1.90	-1.39	.166
	T2	-1.79	-1.17	.243

BDI-II = Beck Depression Inventory Second Edition; IPST = Internet-based Problem Solving Treatment.

8

SUMMARY AND GENERAL DISCUSSION

Depression is common in MS patients and has a considerable impact on quality of life. However, it often remains undiagnosed and undertreated. Early recognition should be improved, and optimal treatment approaches further investigated. The general aims of this thesis were therefore to gain more insight in MS-related depression and its treatment in order to improve quality of care for depressed MS patients. More specifically, we aimed to calculate the prevalence rate of depression in MS, and to investigate the clinical symptom profile of MS-related major depressive disorder (MDD). Further, computer-based screening and treatment possibilities were examined, which mainly concerned investigation of the feasibility and effectiveness of an Internet-based CBT intervention for MS patients suffering from clinically relevant depressive symptoms.

Here, results from the previous chapters will be summarized. In addition, main findings are discussed in relation to the existing literature, and clinical implications and future perspectives will be addressed.

SUMMARY OF THE MAIN FINDINGS

In **Chapter 2,** a systematic review and meta-analysis with a targeted analysis of studies on the prevalence of depression and anxiety in MS was presented. In total, 58 articles with a total sample size of 87,756 MS patients were selected. Pooled mean prevalence was 30.5% (95%CI=26.3%–35.1%) for depression and 22.1% (95%CI=15.2%–31.0%) for anxiety. The weighted prevalence of self-reported clinically significant depressive or anxiety symptoms was higher (35% and 34%) compared with disorders (21%, p=.001 and 10%, p<.001). Prevalence rate of a depressive disorder was relatively lower in studies from Europe compared with studies performed in Northern America, or in other continents. Anxiety disorder was more prevalent in community-based samples compared with samples from clinical settings. No differences in prevalence estimate were observed as a function of study quality, assessment method and prevalence period. However, despite our efforts to adequately enhance quality and decrease study differences, heterogeneity remained considerably high and subgroup analyses did not reveal the sources of heterogeneity making it difficult to predict which study results in which prevalence. Results emphasize the importance to agree on how to define depression and anxiety and how to recruit patients in order to improve prevalence estimates and to clarify their relation to specific patient related factors.

In **Chapter 3** we aimed to investigate the clinical profile of MS-related depression. Results showed only subtle differences in the symptom profile of moderate to severe MDD in MS patients compared with the profile of MDD in patients without MS. The symptom 'future pessimism' was more common in MS patients (OR=1.62, 95%CI=1.02–2.59). 'Diminished capacity for pleasure/enjoyment' (OR=0.44, 95%CI=0.24–0.78), 'increased appetite' (OR=0.40, 95%CI=0.19–0.85), 'arousal symptoms' (OR=0.49, 95%CI=0.28–0.84) and 'panic/phobic symptoms' (OR=0.49, 95%CI=0.29–0.84) were less common in MS patients. Twenty-five symptoms (83%) out of 30, including depression's core symptoms (sadness and loss of interest), were not differentially associated with MS and no differences existed for the symptom clusters (cognitive, somatic, melancholic,

atypical). MDD in MS was characterized by older age of onset (p<.001), and fewer comorbid anxiety disorders (37% versus 72%, p<.001).

In **Chapter 4**, it was shown that a computer-based screening is a feasible way to detect psychological distress in MS-patients in clinical care, and could support MS nurses in their work. Results demonstrated that most patients considered the screening meaningful (n=35/40, 88%) and the system easily usable (n=37/40, 93%). Average completion time of the screening was below 8 minutes. Many patients (n=35/40, 88%) had elevated distress levels, of whom the majority was referred to psychosocial care or rehabilitation. The MS nurse was satisfied with the quality and content of the screening. The screening facilitated her work and helped her to more specifically focus on actual problems to be addressed, including unmentioned problems that could be overlooked easily. A randomized controlled trial with longer follow-up should test whether routine screening, in comparison to routine care, is effective in detecting distress (as depression), and results in appropriate referrals, adequate treatments, and improved outcomes.

The feasibility pilot described in **Chapter 5** showed that an adjusted version of guided Internet-based CBT is a feasible treatment for depressive symptoms in MS patients. Forty-four MS patients with mild to severe depressive symptoms followed an Internet-based problem-solving treatment (IPST). More than half of the patients (52%) completed the intervention and the majority (85%) reported satisfaction with the intervention, which is comparable with similar studies [1],[2]. After the intervention, depressive symptoms had significantly decreased (BDI-II change: mean=-3.9, p=.01, d=0.51 in intention-to-treat analysis; BDI-II change: mean=-9.0, p<.001, d=1.50 in completers analysis). Preliminary findings indicate that guided IPST can reduce depressive symptoms in MS patients, especially in those who report more depressive symptoms at baseline and those who complete the intervention. The results of this pilot study are encouraging and supported the initiation of a randomized controlled trial to investigate the effectiveness of IPST for depressed MS patients.

In **Chapter 6**, the study protocol of the intended randomized controlled trial (RCT) to investigate effectiveness of IPST for depressive symptoms in MS was described.

Finally, results of the RCT on effectiveness of a guided IPST for depressive symptoms in MS patients were presented in **Chapter 7**. In total, 171 patients were randomized to IPST (n=85) or a wait list control (n=86). Early follow-up (T1: within a week after the intervention) was completed by 152 (89%) MS patients, and 4-months follow-up (T2) by 131 (77%) patients. The IPST group and wait list control both showed a large significant improvement in depressive symptoms but no significant difference between groups was found at T1 (d=0.23, 95%CI=-0.17–0.63, p=.259) or at T2 (d=0.01, 95%CI=-0.44–0.46, p=.953). Also no significant difference was found when comparing IPST completers (n=57, 3 or more modules completed) with the wait list control at T1 (d=0.33, 95%CI=-0.11–0.77, p=.136) or at T2 (d=0.05, 95%CI=-0.43–0.53, p=.828).

Additional telephone support (text messages) did not increase compliance rate of the intervention (3 or more modules completed), compared with no telephone support (65% versus 69%, p=.703). There was a significant improvement in depressive symptoms of 66% (n=49/74) in the IPST group and 53% (n=41/78) in the wait list control at T1 (p=.087) and 63% (n=40/64) versus

60% (*n*=40/67) at T2 (*p*=.743). In the IPST group 24% (*n*=18/74) was recovered from depressive symptoms at T1 versus 18% (*n*=14/78) in the wait list control which did not significantly differed (*p*=.335). At T2, 28% of patients (*n*=18/64) was recovered in the IPST group versus 26% (*n*=17/67) in the wait list control (*p*=.722). Results showed there is no indication that IPST for MS patients with moderate or severe depressive symptoms is more effective in reducing depressive symptoms compared to a waiting list.

DISCUSSION OF THE MAIN FINDINGS

Prevalence of depression in MS

In this thesis we showed a 31% prevalence of depression in MS. In line with what one would expect [3], we found that the prevalence of clinically significant depressive symptoms was elevated (35%) compared with the prevalence of depressive disorder (21%). These results add to previously performed reviews reporting high depression rates in MS [4]–[6] and suggest depression percentages are elevated in MS compared with rates in the general population [7]–[11]. This is supported by the first population-based study comparing depressed MS patients with concurrent controls that was recently published [12]. Our results also correspond with the general finding of increased risk of depression when a chronic (neurological) illness is present [3],[13] and approach prevalence estimates of reviews on depression in other chronic medical illnesses like Parkinson's disease and Diabetes [14],[15]. Seemingly, the presence of a disease somehow results in elevated depression comorbidity. However, there is considerable spread in all these estimates due to different study designs which leads to uncertainty about the actual prevalence of depression.

Chapter 2 of this thesis demonstrated that in spite of scrutiny of a number of subgroups, which seemed adequately selected and well-defined, heterogeneity persisted in the depression estimates hampering solid conclusions for the MS population. Explaining heterogeneity and improving prevalence estimates may help to better understand the prevalence of depression in MS and assist clinicians to identify MS patients who are at high risk for depression and require more extensive examination. Explanations for high heterogeneity could be related to methodological limitations of the studies in the existing literature and a number of (untested) factors that varied across these studies. In this context, one could think of differences in methods of depression assessment and of varying patient characteristics. These two issues will be discussed in more detail below.

Assessment of depression

High heterogeneity could be related to variation in depression definition and assessment across studies. MS researchers often do not make the distinction between depression as a symptom or depression as a syndrome. In addition, studies on comorbidity of depressive disorder use many different data sources as medical record review, self-report, interview and administration data.

Information on assessment method is frequently missing in studies, especially when data are extracted from medical records and insurance databases [16].

The most widely used approach by psychiatrist to establish a depressive disorder is the standardised interview which is based on the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) [17] and on the World Health Organization's International Statistical Classification of Diseases and Related Health Problems (ICD-10) [18]. The interviews are performed by trained interviewers. They are valid, use rigorously defined criteria for depressive disorders, and form the bulk of the clinical research on depressive disorders [19]. In our systematic review, only five studies of the included studies used (semi) structured interviews to establish DSM criteria, of which a mere two were rated with good quality. More high quality studies with large population-based samples using diagnostic interviews for the MS population are therefore encouraged [20]. As these studies may require considerable effort and time, it was recently suggested to consider administrative databases with ICD codes to assess depression in large population-based studies. However, clinical details are typically lacking in these databases that are mainly collected for health system management and also their validity for research must still be assessed [21],[22].

A self-report instrument is typically used to screen a large population of patients. It cannot be used to make a formal diagnosis of depression and tend to report higher rates compared with standardised interviews [3], which was also supported by our findings (**Chapter 2**). Still, self-report scales could be used to quickly capture a range of depressive symptoms in MS, or as the first stage of a two-phase survey which also includes a diagnostic interview to determine actual cases of depressive disorder in MS [3],[23]. Variation in and the appropriateness of self-report scales and cut-off scores to assess clinically significant symptoms may however have further contributed to high heterogeneity in prevalence rates presented in **Chapter 2**. Applied self-report scales were not always validated for the MS population and often contained a number of questions related to physical symptoms of MS such as fatigue, sleep problems, and pain. Including these items could increase the score simply because a physical illness is present [5].

The American Academy of Neurology Guidelines advised the Beck Depression Inventory (BDI) to detect depression in MS [24]. This self-report instrument is validated for the MS population and most widely used in MS research. Since sufficient evidence for other existing instruments to measure depression in MS was lacking [24], recent studies by Patten *et al.* (2015) [25] and Fischer *et al.* (2015) [26] validated various self-report depression scales against clinical diagnoses of MDD in MS patients and provided appropriate cut-offs. The Center for Epidemiologic Studies Depression scale (CES-D) [27], Hospital Anxiety and Depression Scale (HADS) [28], Patient Health Questionnaire (PHQ-9) [29], Inventory of Depressive Symptoms (IDS-SR) [30] and BDI-II [31],[32] demonstrated good accuracy, but all have their own advantages and disadvantages [25],[26]. The BDI is mostly used, but is copyrighted. The PHQ and IDS-SR are widely used instruments, freely available and translated in many languages, making them particular interesting to screen and quantify depression in MS. Brevity of the PHQ is suggested to enhance the feasibility of its use [25]. The IDS-SR covers all DSM-IV criteria, and offers a self-rated validated 16-item short version. The

IDS-SR is increasingly used, and applied in large longitudinal (no MS) cohort studies [33]. Subscales for cognitive and somatic symptoms can be constructed [34] and algorithms for identification of melancholic [35], or atypical depression [36] are available. Atypical and melancholic subtypes of MS-related depression were lately suggested to be relevant to elucidate biological substrates of depression in MS [26],[37].

In addition to the studies above, findings from **Chapter 3** support the idea that different instruments to identify depression that are used in depressed patients without MS could be used to assess depression in MS, as the depressive symptom profile does not seem to differ substantially between depressed patients with and without MS. It may be time to move towards a consistent approach to identify and measure psychiatric comorbidity in MS to improve comparability of prevalence rates [4],[24].

Patient characteristics

Heterogeneity may be also hidden in specific patient related factors such as age, gender, MS course, duration, and severity. However, studies often lack adequate information about these factors and/or are mixed in their conclusions regarding presence of depression and these clinical and disease characteristics [5],[38]. For example, there is evidence suggesting prevalence of depression to be higher among patients with progressive forms of MS compared with those with relapsing remitting MS (RRMS) independently of disease duration and physical disability [39]. Primary progressive (PP) MS is possibly more distressing for patients, also because it is considered a primary neurodegenerative disease with a different pathogenesis. On the contrary, other studies found that patients with PPMS had lower life time risk of MDD compared with RRMS patients, suggesting the inflammatory component of RRMS course may be associated with elevated depression [40], or found no association with disease course at all [41],[42]. Some studies found younger age, or greater extent of functional limitation to be predictive of more depressive symptoms [41],[43]. Longer [43] but also shorter [41] duration of MS were found to increase the risk for depressive symptoms. Other studies found no difference in MS duration, age or disease severity for patients with or without depression [42],[44]. Some studies indicated different prevalence rates for women and men [12],[45], but other suggested that depression is equally prevalent in both [43].

These findings may be inconsistent due to diversity of MS itself. MS is not a homogeneous and constant disease thus resulting in large variability between patients. Patients with similar MS durations could have very different disease courses, relapse rates, and cerebral and spinal involvement, each having a potentially different effect on mood. In addition, the important determinant of depression may be just as well related to the way MS patients adjust to adversity [38]. Furthermore, heterogeneity in prevalence rates of depression may be partly explained by depression-related variables that were not assessed, such as number of depressive episodes, onset, and duration. In addition, there may be MS or depression related factors we are not aware of. All these differences in case mix between studies may cause unexplained variability, and make it difficult to predict, rate and explain depression in MS. This case mix factor is however difficult to control and more extensive disease information of individual patients is required.

For now, although this may seem trivial, the first step to further clarify variation in prevalence of depression in MS would be to conduct more high quality studies with sound designs. These studies should include representative study populations and report patient related variables like age, sex, and disease-specific estimates for different geographical regions, and use common and validated methods such as the BDI, PHQ-9 or IDS-SR to assess depression in MS. In addition, measurement of key data elements such as sex, race/ethnicity, clinical course, comorbidity and MS diagnostic criteria and outcome measures must be harmonized to facilitate pooling and comparison of study findings [21]. Next to consistent subgroup analyses, analyses with a more multivariate approach could then be used to examine (more) sources of heterogeneity in the prevalence of depression in MS taking into account different patient (MS) related factors [46]. As lack of access to individual patient data is a common limitation, researchers may consider proceeding to individual patient meta-analyses.

The concept of depression in MS

Research on the clinical profile of depression in MS is still scarce. Earlier publications have been inconsistent, and were generally based on small samples and self-reported depression [47],[48]. In **Chapter 3** of this thesis we therefore compared the depressive symptom profile of moderate to severe MDD in patients with MS with moderate to severe MDD in patients without MS. It appeared that MDD in the context of MS has a similar symptom presentation and refers to the same concept as MDD where no underlying medical illness is present. MDD in MS patients was, however, characterised by later onset and less comorbidity and anxiety distress which may suggest a purer form of MDD. Our results replicate recent findings of a similar clinical phenotype of depression in patients with and without MS [47] and are in line with literature that showed similar symptom profiles in other depressed groups consisting of immigrants [49] or diabetes patients [50]. Apparently, a clinical depression is phenomenologically robust and remains diagnostically valid among psychiatric as well as medical samples.

MS-related pathways

Although the symptom profile of MDD patients with MS is similar to MDD patients without MS, it is unknown whether underlying similar aetiological mechanism are involved. Knowledge on the aetiology of MDD is limited and complex, but diverse gene-environment interactions, endocrine, immunologic and metabolic mediators, and cellular, molecular and epigenetic forms of plasticity are suggested to play a role [51]. In MS, MDD pathophysiology might be overlapping with that of many psychiatric patients, as damage to the hippocampus, HPA-hyperactivity and chronic neuroinflammation are present in both groups [51]–[54]. Since most of these studies are cross-sectional, more longitudinal research on the behavioural, genetic and biological (e.g. neurodegeneration, enhanced peripheral immune activation) factors influencing MS and depression could improve our understanding of the pathways involved. New technologies such as magnetic resonance imaging may help to explain neuroanatomic links between depression and changes in the central nervous system due to MS [21]. Results from **Chapter 3** suggest MDD in MS may be a purer form of MDD which might be due to the presence of a brain disease with

specific MS-related brain abnormalities related to MDD. In that case, examining neurobiological correlates of MS-related MDD and other disease-related factors perhaps contributes to an increased understanding of the pathogenesis of MDD in general.

Course of depression

Although the symptom profile of MDD patients with MS is similar to MDD patients without MS, MS-related MDD may display a different course. MDD in patients without MS is considered an episodic disease where depressive episodes can come and go over time [55]. Although longitudinal research on depression in MS has only been performed to a limited extent, findings point towards depressive symptom rates that remain high, static and chronic over time and do not remit spontaneously [42],[56]–[58]. Clinically relevant depressive symptoms at baseline was strongly related to the risk of depression at follow-up [42] and around 2/3 of MS patients with substantial depressive symptoms at baseline were depressed at 10 year [58]. When depression in MS is more chronic, this could implicate that it is not simply a reaction to the diagnose of MS or reaction to worsening of MS as one would expect improvement over time [42]. Absence of fluctuations in depressive symptoms could reflect inflammatory dysregulations and/or damage to the central nervous system that are characteristic for MS [5],[42]. This suggestion is supported by studies on depression in the general population that found certain inflammatory dysregulations among those with more chronic forms of depression [59].

Symptom profile and MS characteristics

As the MS-related MDD profile is similar compared with MDD patients without MS, one may be tempted to think that MS characteristics do not have any effect on the presentation of depression in MS. However, the relation between disease characteristics and differences in symptom profile were not explicitly assessed. As a result we do not know whether the MDD symptom profile itself is influenced by MS characteristics and it may still differ within the MS group. Depression characteristics and phenomenology at MS onset may be different compared with characteristics later in the disease, during relapses and different cerebral involvement, or at particular stages (e.g. when RRMS changes into SPMS and MS is definitely becoming progressive). For example, SPMS patients tend to demonstrate more depressive thought such as hopelessness than RRMS patients [60]. A review revealed a more specific association between MS lesion location and affective symptoms and somatic complaints, but not with cognitive distortions [5],[61]. And abnormalities in both the limbic and endocrine system may be more closely related to affective and cognitive depressive symptoms in MS [52],[62], whereas MS-inflammatory markers showed stronger correlations with somatic symptoms [54],[62]. Various mood-related symptoms (sadness, irritability) in MS are suggested to fluctuate more over time than somatic symptoms (sleep, appetite) and evaluative symptoms (feelings of guilt and worthlessness) [63]. However, there is inconsistent evidence whether depressive symptom fluctuations correlate with disease relapse, course and physical disability [42],[57]. Replication of our findings on the MS-related symptom profile is therefore required in different MS samples (inpatients, nursery homes, clinics, general population) that vary in onset, course, and MS-disability and at different moments in time (longitudinal).

Treatment for depression in MS

Internet-based treatment

Depression in MS is often not adequately treated. Research on mental health interventions for depressed MS patients is still in its infancies, and treatment guidelines for depression in MS do not yet exist [24],[64]. A standard easily accessible and low-intensity Internet-based problem-solving intervention (IPST) was expected to be a suitable candidate for the MS population to overcome treatment barriers. Results of the pilot study presented in **Chapter 5** provided evidence for the feasibility of IPST for depressed MS patients (BDI-II ≥16) and a significant reduction of depressive symptoms after the intervention. Subsequently, a high-quality trial was designed (**Chapter 6**) and performed to investigate the effectiveness of IPST for moderate or severe depressive symptoms in MS. Results described in **Chapter 7** demonstrated that MS patients treated with guided IPST showed a large decrease in depressive symptoms that sustained over four months follow-up. However, a similar improvement was observed in the wait list control, and it was concluded that a 5-week self-help IPST has no additional value to a waiting list.

The considerable decrease in depressive symptoms in the wait list control was unexpected and several explanations were suggested in **Chapter 7**. It was for example attributed to recruitment of highly motivated patients that are willing to address their complaints, resulting in improvement. A small degree of contact with a clinician (e.g. interview), inclusion and assessment of patients in our trial could have improved outcomes [65] and/or facilitated awareness of complaints leading to beneficial effects such as seeking help in different ways. Decreased depression symptomatology in the wait list control could also be a result of 'regression to the mean' as high scores are typically more likely to decrease.

There is no reason yet to conclude that ICBT cannot be a helpful (additional) intervention for the depressed MS population and overcome treatment barriers, particularly given findings of its effectiveness in two trials on ICBT for depression in MS [66],[67]. Results from these studies correspond to results found for non-Internet-based CBT for depression in MS [68],[69], and with literature on ICBT for depression in general [70]. However, as we found no indication that IPST is more effective than a waiting list, findings on ICBT for depression in MS should be considered inconsistent and more research is therefore needed. In addition, potential advantages of different or more extensive ICBT interventions should be investigated, as well as a combination of ICBT with face-to-face psychotherapy or other treatments [71]. Next to that, it should be further explored if and how this treatment should be adapted to this particular population [72],[73] and which MS patients could profit from Internet-based intervention, in what form (guided, blended, automatic, personalized) and in what intensity. Finally, treatment adherence should have our attention as very little is still known about which patients stop treatment, at what moment in time, and under which circumstances (e.g. recovery, deterioration, not acceptable) [74].

In future research, we may need to temper our expectations of treatment outcomes, as it was recently suggested that effectiveness of psychotherapy or medication treatment for depression has been overestimated. High quality psychotherapy studies show smaller effects than was previously suggested and some reserve is therefore appropriate [75].

Clinical improvement and recovery

The overall improvement in depressive symptoms in the study population of the RCT presented in **Chapter 7** could have represented the natural course of depressive symptoms in MS patients. In the general population, half of depressed patients recovers within three months [55]. More than half of the included MS patients demonstrated significant improvement in depressive symptoms at follow-up assessments and around 25% of this group fully recovered. This recovery percentage is relatively low and supports the aforementioned suggestion of a more chronic course of depression in MS. Still, a subgroup of depressed MS patients reached remission and many showed clinical significant improvement in depressive symptoms. It is known that people could profit from their own adequate emotional, social and medical support systems and react with resilience to major (disease) events, and show recovery after initial distress [76]. In MS, a period of grieving and depression could be considered normal given the accumulation of irreversible losses patients face [73],[77]. Accordingly, not all depressed MS patients that were included in our trial may have interpreted their depressive symptoms as a problem; meeting criteria for clinical relevant depression does not have to imply a need for formal mental health care [78]. Actively providing treatment to patients that are resilient or without a specific need for help will then lead to overtreatment and unnecessary medicalization, stressing the importance to distinguish between adaptive (negative) emotions that improve over time and persisting emotional disorders with a true need for formal mental health care.

The majority of MS patients in our trial showed persistent residual depressive symptoms and did not recover which could increase the risk of relapse and poor functional and psychosocial outcomes [79]. Non-recovery could be due to high depression severity at baseline [42], to the low intensity e-health intervention, or might have to do with the MS-related depression itself that is suggested to be static and more difficult to treat [42],[80]. Mohr *et al.* (2001) found that the majority of MDD patients treated with 16-week CBT, group therapy or antidepressants remained refractory to treatment and continued to meet criteria for MDD after 16 weeks of treatment [80]. In another trial, 75% of MS patients with clinical significant depressive symptoms at baseline (BDI>13) did not show recovery after a 9-week ICBT [67] which is similar to recovery findings in our pilot study (70%) [81] and the treatment arm of our trial (76%) [82]. A single (e-health) intervention might than not be sufficient for this patient group and combined treatment options need to be considered. Also one may speculate that full recovery is not realistic for many MS patients due to the presence of a chronic progressive disease where symptoms overlap and biological and psychosocial changes are continuously involved. Poor treatment response may indicate evidence of an aetiologically different subtype of depression in which inflammatory dysregulation plays an important role. Research has shown that inflammation may be associated with poor response to pharmacotherapy for depression, which in turn may contribute to a more chronic course of depression [83]. As inflammatory dysregulations are characteristic for MS patients, this patients group may not fully benefit from regular treatments. It is suggested that alternative treatments as anti-inflammatory medication or exercise may be better able to improve depression when inflammatory dysregulations are present [84]. It is therefore essential to further identify and understand non-recovery of depressed MS patients and adjust treatment accordingly [55],[85],

as well as to provide an accurate and feasible method to distinguish them from depressed MS patients that do recover over time without treatment.

Clinical implications and future perspectives

Due to the highly variable, unpredictable and chronic course of MS, patients with MS will face different challenges to physical, social and psychological well-being resulting in various needs, frequently over a period of many years [86]. Integrated approaches of patients management and formation of multidisciplinary teams in many branches of medicine have improved access to psychological care for these kind of patients [19]. However, MS research is still not extensive enough to guide recommendations about how to assess and manage depression in MS [24].

Diagnostics

In order to provide effective treatment for depression, depressed MS patients should first be identified. As the clinical profile of depression remains valid among MS patients, the signs, symptoms and also the instruments to identify depression that have been developed in mental health care can be used among MS patients. In further clinical diagnostic assessment, the patient's current circumstances and symptoms, and biographical and family history can be further assessed by a trained clinician or psychologist. MS itself should be included in the differential diagnosis, especially in patients with atypical features of depression, who lack response to regular psychological treatment [87].

This thesis does not resolve the challenges in diagnostic evaluation of individual patients posed by the overlap between psychiatric and neurological symptoms and their different causes. It is still unclear if and in what way depression is a reaction to MS and/or integral to inflammatory and degenerative brain changes associated with MS [5]. Ways to disentangle depression from somatic illness and disability is complicated and may even come at the cost of a comprehensive attitude towards the disease. Overlapping symptoms of depression that are related to MS symptoms and pathophysiology (neurodegeneration, inflammation) may be even of extra relevance to the syndrome of depression as it occurs in MS patients [88]. Overlapping psychiatric and neurological symptoms should then not be viewed as two different comorbid entities but as inseparable lying in the grey area between psychiatry and neurology. As psychiatry and neurology are separate medical specialties it is tempting to disentangle complex brain disorders as MS and depression into marked categorizations that are based on single symptoms. Instead, dual complexities of MS and depression may require more integral diagnostics and a closer collaboration between neurologists on the one hand and psychiatrist and psychologist on the other hand in order to offer adequate interpretation and treatment selection for the psychiatric aspects of MS [89],[90]. In doing so, clinicians should assess their patients carefully and differentiate those with MS or depression as their sole problem, while remembering that there will be those who seem to have both at the same time [91].

Treatment

In depressed MS patients with adequate emotional, social and medical support systems, and with a lack of significant suffering or a need for treatment, depression may recover due to patients' self-relience. For these patients, a proper balance between support in their self-reliance and their need for professional care is advised [78]. When depressive complaints are not present for long, patients may benefit from a period of watchful waiting. For the group of MS patients that experiences significant impact from their depression, and experience no improvement after a waiting period, formal care should be available. Given the proposed complexity of MS-related depression, this patient subgroup may need a more intensive multimodal treatment approach with adaptations to specific needs and characteristics of MS patients [5] to maximize effectiveness. However, we still do not know which patients will receive the greatest benefit from this approach. Standard depression guidelines should therefore be followed until more specific guidelines for depression in MS are provided taking into account MS specific conditions (inflammatory component, physical problems, cognitive impairment) and specific needs of MS patients. In addition, research should focus on interactions between patient variables, treatment modalities, and their outcomes [21].

Individual patient monitoring

More individual discrimination between (depressed) MS patients could provide clues for underlying mechanisms, phenomenology, prognosis, diagnosis and (tailored) treatment of depression in MS and could improve outcomes for the individual patient. It is still unknown which MS patients with a particular combination of characteristics (course, severity, duration) are at risk to develop depressive symptoms or MDD, at what moment in time and under which circumstances. When depressed, information is lacking on how the depressive symptom profile develops over time and how it is related to the disease process. Which of these patients will recover spontaneously or remain depressed, and what specific treatment should be selected?

Ecological momentary assessment (EMA) is a frequent sampling method of patients' behaviour and subjective experience in real-word contexts [92]. EMA research may provide more information about depression determinants, individual variation over time and interplay with the environment and MS-related factors. Although practical, statistical and technical short comings need to be considered, this technique promises that patients can be profiled, and that subtypes of patients groups can be distinguished based on a combination of variables such as gender, age, and disease characteristics [92],[93]. The resulting, specific risk profiles could help clinicians to decide when they should be extra alert and/or intervene in particular stages of the disease process. When extended with biological information, such a method may facilitate better understanding of the interplay between depression and MS, and improve diagnostics, monitoring and enhanced (tailored) treatment selection. However, this technology is not yet widespread available, is rapidly developing and will pose new challenges and obstacles.

Homo digitalis

Technological developments in for example EMA, virtual reality, mobile applications (e.g. smartphones, smartwatches, Google glass), avatars, serious gaming, automatic emotion recognition

and various Internet-interventions, will have a major and probable lasting impact on the field of mental health care [94]. These technological innovations arise extremely rapidly and are often warmly welcomed due to expected financial gains. They allow the relatively easy collection of more and new data regarding patient characteristics and mental health using GPS data, social media and the registration of social, physical and online activity. This may however come at the cost of proper reflection on the ethical consequences and of a (political) debate on our relationship with technology. We risk to blindly apply and use these innovations simply because they are available. However, governments and commercial parties have access to many of these data and borders of personal and public domain will fade jeopardising privacy and personal integrity [95],[96]. Although these innovations can be of great help in detecting psychological complaints and provide (tailored) support to the patients' needs, we should also ask ourselves to what extent we want to move towards a world in which all behaviour will be controlled by technology. When we can predict, prevent and control all our emotions and dysfunctional behaviour, depression will not necessarily be eradicated; it will then become nothing more than a bug in the technological system. We should therefore not lose sight of the aims, reasons and consequences of technology that is applied to our patients and keep on reflecting on the advantages and disadvantages of the new technological possibilities offered to us.

Closing remarks

The research field of comorbid depression in MS has evolved greatly in the recent years making it a very interesting and dynamic research area. This thesis contributed to the improvement of recognition and treatment of depression in MS against the background of recent technological developments. There are still many challenges ahead as comorbidity of depression and MS is complex and interacts on different levels. If research is to progress, we should expand our understanding of specific characteristics of MS-related depression, interactions between patient variables and indications for psychological interventions. This will further increase our ability to effectively improve the quality of life for patients with MS making the future at least a bit more hopeful for those affected by a somatic disease for which there is currently no cure.

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SAMENVATTING

Dit proefschrift gaat over depressie bij mensen met multiple sclerose (MS). Hoe vaak komt depressie voor bij mensen met MS? Ziet een depressie er hetzelfde uit bij mensen met en zonder MS? In hoeverre kunnen technologische (computer) ontwikkelingen bijdragen aan tijdige herkenning en behandeling van depressieve klachten bij deze doelgroep? Een groot deel van dit proefschrift betreft het onderzoek naar de vraag of kortdurende cognitieve gedragstherapie via internet een haalbare en effectieve methode is om depressie bij mensen met MS te behandelen. Hier worden de achtergrondinformatie en de resultaten samengevat.

Multiple Sclerose

Multiple Sclerose (MS) is een chronische ziekte waarbij ontstekingen optreden in het centrale zenuwstelsel (hersenen en ruggemerg). Kenmerkend is neurodegeneratie en demyelinisatie: een proces waarbij de beschermende laag (myelineschede) van de zenuwcel wordt aangetast. Hierdoor raakt de prikkelgeleiding in de zenuw verstoord, waardoor men last kan krijgen van allerlei neurologische klachten, zoals krachtverlies, vermoeidheid, spasmen, spraakproblemen, zichtproblemen, concentratie- of geheugenstoornissen, pijn, blaasproblemen, en seksuele klachten. Hoewel de uitingsvormen en het beloop van MS sterk variëren, gaan de meeste mensen achteruit in de loop van de tijd. Er bestaat vooralsnog geen behandeling die MS geneest. Behandeling richt zich met name op het verminderen van de symptomen en het afremmen van de progressie van MS. De precieze oorzaak van MS is nog onduidelijk, maar waarschijnlijk ontstaat MS in een complex samenspel van erfelijkheid en omgevingsfactoren.

Wereldwijd hebben ongeveer 2,5 miljoen mensen de diagnose MS. In Nederland geldt dit voor 1 op de 1.000 inwoners. MS treft veelal jonge volwassenen (20–40 jaar) in de bloei van hun leven, en komt vaker voor bij vrouwen dan bij mannen. Naast ziekte gerelateerde problemen en een onzekere maar ongunstige prognose worden mensen met MS ook nog eens geconfronteerd met onzekerheid en problemen in het gezin, in sociale contacten, en op het gebied van werk en financiën. Het is daarom geen verrassing dat deze patiëntenpopulatie een verhoogd risico heeft om depressieve klachten of zelfs een klinische depressie te ontwikkelen.

Depressie

Een depressie is een heterogeen syndroom met verschillende uitingsvormen. Volgens het diagnostisch handboek van de psychiatrie ('Diagnostic and Statistical Manual of Mental Disorders', of kortweg: de DSM) is sprake van een depressieve stoornis wanneer iemand langer dan 2 weken bijna dagelijks het grootste deel van de dag een sombere stemming of verlies van interesse en plezier heeft. Daarnaast moeten nog andere symptomen aanwezig zijn, zoals slaapproblemen, concentratieproblemen of besluiteloosheid, weinig energie, vermoeidheid, traagheid of lichamelijke onrust, terugkerende doodsgedachten, minder of juist toegenomen eetlust of gewichtsverandering, gevoelens van schuld of waardeloosheid. Deze klachten moeten bovendien een duidelijke lijdensdruk geven of iemands functioneren in het dagelijks leven verstoren. De ernst van een depressie kan variëren van licht tot zeer ernstig – hoe meer symptomen, hoe ernstiger de

depressie. Het is nog onbekend wat de precieze oorzaak van depressies is, maar vaak gaat het om een combinatie van genetische, biologische, sociale, psychologische en omgeving gerelateerde factoren. Depressie staat wereldwijd bekend als een belangrijk gezondheidsprobleem en draagt sterk bij aan de wereldwijde ziektelast.

Multiple sclerose en depressie

Mensen met zowel MS als depressieve klachten hebben een extra hoge ziektelast: zij ervaren nog meer belemmeringen in het dagelijks functioneren en hebben een lagere kwaliteit van leven. Naast de directe weerslag op de kwaliteit van leven, kunnen depressieve klachten bij mensen met MS het ziekteproces negatief beïnvloeden en het omgaan met de (gevolgen van) de ziekte nog eens extra bemoeilijken. Vooralsnog is onduidelijk in hoeverre depressieve klachten een reactie zijn op de aanwezigheid van een chronische ziekte met een onvoorspelbaar beloop, of een gevolg van dezelfde (neuro-)biologische en genetische factoren die ook tot MS leiden.

De constatering dat depressie bij mensen met MS beduidend vaker voorkomt dan in de algemene bevolking is reden tot zorg. Maar hoe vaak komt depressie dan voor bij mensen met MS? De verhoogde prevalentie aantallen uit de literatuur variëren flink: tussen 14% en 54%. Dit is mogelijk te wijten aan methodologische kwesties zoals verschillen in de grootte, samenstelling en herkomst van de onderzochte populatie, of in de meetmethode die is gebruikt om de (ernst van de) depressie vast te stellen. De betrouwbaarheid van veel studies is verminderd doordat men een klinische depressie gemeten heeft met een vragenlijst in plaats van met een diagnostisch interview, of zich heeft gebaseerd op een relatief klein aantal proefpersonen. Er bestaat dan ook behoefte aan duidelijkheid over hoe vaak mensen met MS óók een depressieve stoornis hebben (of klinisch relevante depressieve symptomen) en over de redenen voor de variërende percentages in bestaande studies. Dit was de aanleiding voor het eerste deel van dit proefschrift: een kwantitatieve samenvatting van bestaande studies naar de prevalentie van depressie en angst bij mensen met MS.

Hoe vaak depressie en angst voorkomen bij MS

Hoofdstuk 2 beschrijft een systematische literatuuroverzicht en meta-analyse. Via diverse zoekmachines (PubMed, EMBASE, PsycINFO) werd een uitgebreide zoektocht verricht in de wetenschappelijke literatuur over depressie en angst bij mensen met MS. In totaal werden 58 studies geselecteerd, gebaseerd op 87.756 mensen met MS om een schatting te maken hoe vaak depressie voorkwam. Hierbij werd rekening gehouden met de kwaliteit van de studies, de definitie van depressie, alsmede de populatie en regio waaruit men deelnemers geselecteerd had.

De gewogen gemiddelde prevalentie bij mensen met MS was 30,5% voor depressie (95% betrouwbaarheidsinterval (BI)=26,3%–35,1%; *n*=58 studies) en 22,1% voor klinisch relevante angst (95%BI=15,2%–31,0%; *n*=15 studies). Studies die zich baseerden op zelfrapportage vragenlijsten van klinisch relevante symptomen bleken hogere prevalenties te vinden dan studies die een klinische diagnose van depressie of angst gebruikten (respectievelijk 35% versus 21%, *p*=0,001 en 34% versus 10%, p<0,001). De prevalentiecijfers van depressie bij mensen met MS was lager in Europese studies dan in studies afkomstig uit andere landen. Angststoornissen

werden vaker gevonden bij mensen met MS uit studies onder de algemene bevolking dan bij mensen die deelnamen aan studies van/in ziekenhuizen. In alle gevallen was de heterogeniteit van de gerapporteerde prevalentie aanzienlijk zonder dat daarvoor een duidelijke verklaring werd gevonden. Hierdoor is het niet mogelijk een precieze prevalentieschatting te geven van depressie en angst bij mensen met MS, oftewel, het blijkt lastig te voorspellen welke studie in welke prevalentie resulteert. Dit alles leidde tot de conclusie dat bestaande studies wijzen op een hoge prevalentie van depressie en angst (zowel symptomen als stoornis) bij MS, maar dat verder onderzoek naar de bronnen van heterogeniteit noodzakelijk is.

Toekomstig onderzoek zou meer aandacht kunnen besteden aan individuele patiëntkenmerken (bijv. sekse, leeftijd, MS-type, ziekteduur, fysieke beperking) en rekening kunnen houden met gelijksoortige definities van depressie en angst, en manieren van werving van deelnemers. Daarmee kan in de toekomst hopelijk preciezer worden vastgesteld welke persoon met MS het hoogste risico loopt om depressief of angstig te worden, zodat tijdig ingegrepen kan worden, dan wel klachten in de gaten gehouden kunnen worden.

Depressieve stoornis met en zonder MS: verschillend of hetzelfde?

Er bestaat geen consensus over hoe depressie bij mensen met MS het beste gemeten kan worden. De overlap tussen psychologische en neurologische symptomen vormt een grote uitdaging voor de kwantificering van depressie bij mensen met een neurologische ziekte zoals MS. Zo kunnen vermoeidheid, slaapproblemen, psychomotorische traagheid, en concentratie- of geheugenstoornissen horen bij MS, maar tevens onderdeel zijn van een depressie. Naast MS symptomen zouden neurobiologische processen die MS (klachten) veroorzaken een belangrijke rol kunnen spelen in hoe een depressie zich uit bij mensen met MS, en zo het klinische fenotype (mede) kunnen bepalen. Onderzoek naar het klinische profiel van een MS gerelateerde klinische depressie is echter schaars. Het tweede doel van dit proefschrift was daarom te onderzoeken hoe het symptoomprofiel van een depressieve stoornis eruitziet bij mensen met MS.

Hoofdstuk 3 beschrijft een vergelijking van symptoomprofielen (op basis van de symptoomclusters cognitief, somatisch, atypisch of melancholisch, en 30 losse depressieve symptomen) tussen mensen met een matig of ernstig depressieve stoornis én MS (*n*=83) en mensen met een matig of ernstig depressieve stoornis zonder MS (*n*=782). Deze twee groepen bleken te verschillen in die zin dat de depressieve personen met MS ouder waren (gemiddeld 48 jaar versus 41 jaar, p<0,001), en minder vaak een comorbide angststoornis hadden (37% versus 72%, p<0,001) dan de depressieve personen zonder MS. Er werden geen groepsverschillen gevonden voor de vier symptoom clusters. Ook waren 25 van de 30 symptomen (83%), inclusief twee van de kernsymptomen van depressie (somberheid en verlies van interesse), niet verschillend gecorreleerd met MS. Wel werden enkele kleine verschillen gevonden in de symptoomprofielen tussen beide groepen. Depressieve mensen met MS rapporteerden vaker 'pessimisme over de toekomst' (OR=1,62; 95%BI=1,02–2,59). Vier andere symptomen rapporteerden ze juist minder vaak dan depressieve mensen zonder MS, namelijk 'toegenomen eetlust' (OR=0,40; 95%; BI=0,19–0,85), 'verminderde capaciteit voor plezier/genieten' (OR=0,44; 95%BI=0,24–0,78), 'opwinding' (OR=0,49; 95%BI=0,28–0,84) en 'paniek/angst' (OR=0,49; 95%BI=0,29–0,84). Dit leidde tot de

conclusie dat het symptoom profiel van depressie niet substantieel verschilt tussen mensen met en zonder MS. Dit betekent dat de uitingsvorm en ernst van depressieve klachten bij mensen met MS met dezelfde vragenlijsten gemeten kan worden als in de algemene bevolking (zonder MS). De verminderde aanwezigheid van angst bij depressieve mensen met MS zou er tot slot op kunnen duiden dat deze groep een 'puurdere' vorm van depressie heeft.

Screening

Het vroegtijdig herkennen en behandelen van depressieve klachten kan de kwaliteit van leven aanzienlijk verhogen. Helaas blijkt dat depressie bij MS regelmatig over het hoofd wordt gezien. Er zijn zelfs indicaties dat klinisch relevante depressie bij meer dan de helft van de mensen met MS niet herkend wordt. Dit kan komen door de overlap van neurologische en psychologische symptomen zoals reeds eerder genoemd. Een andere verklaring is dat mensen met MS hun depressieve klachten zelf als onderdeel van de ziekte zien, of ze niet durven te melden. Een Amerikaanse onderzoeksgroep (White *et al.*, 2008) adviseerde met oog daarop eerder om regelmatig en actiever psychologische klachten te 'screenen' tijdens elk ziekenhuisbezoek. Hoofdstuk 4 beschrijft de opzet en resultaten van een pilotstudie waarin de haalbaarheid van een kortdurende screening via een 'touchscreen' computer onderzocht werd. In totaal werden 43 mensen met MS gescreend middels 67 vragen over depressie, angst, vermoeidheid, cognitief en lichamelijk functioneren. Deelnemers beantwoordden deze vragen op een touchscreen computer voorafgaand aan hun afspraak met de MS-verpleegkundige, die direct toegang had tot de screeningsresultaten. Het invullen van de vragenlijst bedroeg gemiddeld maximaal 8 minuten. De meesten vonden de screening zinvol (*n*=37/40; 93%) en het systeem makkelijk in gebruik (*n*=35/40; 88%). Velen (*n*=35/40; 88%) hadden klinisch relevante klachten op een van de vragenlijsten. Deze deelnemers bleken veelal verwezen te zijn naar passende hulp voor hun klachten, zo bleek uit retrospectief onderzoek. De MS-verpleegkundige gaf aan enthousiast te zijn over de methode: de screening vergemakkelijkte de werkzaamheden en maakte het mogelijk om direct gerapporteerde klachten bespreekbaar te maken, die anders mogelijk over het hoofd waren gezien. Een dergelijke 'screening' methode lijkt het dus mogelijk te maken om psychologische klachten als depressie tijdig te herkennen bij patiënten. Verder onderzoek, in de vorm van een gerandomiseerde gecontroleerde studie met lange termijn metingen, zal moeten uitwijzen of routinematige screening inderdaad beter is dan de gebruikelijke zorg en effectiever om depressie te detecteren en adequater te verwijzen en te behandelen.

Behandeling

Gezien het hoge percentage mensen met MS en depressieve klachten en de goede behandeleffecten van medicatie en/of psychologische behandeling (bijvoorbeeld cognitieve gedragstherapie; CGT), is het opmerkelijk dat depressie in deze groep vaak onderbelicht en onbehandeld blijft. Men vermoedt dat dit niet alleen te maken heeft met het stigma rondom psychologische problemen, maar ook met ziekte-gerelateerde barrières als vermoeidheid, fysieke verslechtering en transportproblemen waardoor behandeling in de vorm van 'face-to-face' gesprekken mogelijk niet volstaat. In de afgelopen jaren zijn daarom alternatieve behandelvormen onderzocht

zoals therapie via de telefoon. De laatste jaren heeft het onderzoek naar en aanbod van online behandelingen een vlucht genomen. Voor standaard online depressie therapie zijn reeds goede resultaten geboekt. Het vermoeden is dat internetbehandeling ook, of juist, voor mensen met MS en depressieve klachten uitkomst kan bieden. Meer specifiek werd verwacht dat een kortdurende CGT aangeboden via internet een geschikte –want laagdrempelige en makkelijk toegankelijke– behandeling zou kunnen zijn voor deze doelgroep. Het tweede gedeelte van dit proefschrift gaat in op de haalbaarheid en effectiviteit van de online zelfhulpinterventie 'Minder Zorgen' voor mensen met MS en klinisch relevante depressieve klachten. De hoofdstukken 5, 6, en 7 beschrijven achtereenvolgens een pilotstudie, een studieprotocol, en een gerandomiseerde gecontroleerde studie naar de effectiviteit van deze interventie. 'Minder Zorgen' is gebaseerd op probleemoplossende therapie (een vorm van CGT) en beslaat 5 lessen waarin de aangeboden informatie, voorbeelden en oefeningen zijn toegespitst op mensen met MS. Tijdens de interventie en het maken van opdrachten worden deelnemers via een website ondersteund door hun coach.

Pilotstudie

Aan de pilotstudie namen 44 mensen deel met MS en milde tot ernstige depressieve klachten. Ruim de helft (52%) maakte de interventie af. Deze mensen hadden gemiddeld meer depressieve klachten bij de voormeting. De geruime meerderheid gaf aan tevreden te zijn over de interventie (88%); deze percentages zijn vergelijkbaar met eerder onderzoek. Deelnemers lieten na afloop gemiddeld een afname zien van depressieve klachten, gemeten met de 'Beck Depression Inventory-II' (gemiddelde afname=-3,9; p=0,01; d=0,51). Deze afname was het sterkst bij de mensen die de interventie hadden afgemaakt (gemiddelde BDI-II afname=-9,0; p<0,001; d=1,50). Geconcludeerd werd dat begeleide zelfhulp voor depressieve klachten via internet haalbaar is bij mensen met MS. De voorlopige resultaten deden tevens vermoeden dat depressieve klachten door de interventie kunnen afnemen, vooral bij de mensen met meer depressieve klachten die de interventie afmaken. Een gerandomiseerd gecontroleerd onderzoek met lange termijn metingen moest echter uitwijzen of dit klopte. In hoofdstuk 6 wordt het protocol en de achtergrond van deze gerandomiseerde studie gepresenteerd. Hoofdstuk 7 beschrijft vervolgens of de interventie 'Minder Zorgen' effectiever is dan afwachten.

Gerandomiseerde gecontroleerde studie

171 mensen met MS en matige tot depressieve klachten werden 'random' toegewezen aan de interventie (n=85) of de wachtlijst (n=86). De belangrijkste uitkomstmaat, depressieve klachten, werd gemeten met de 'Beck Depession Inventory-II (BDI-II)' voor de interventie (T0), na de interventie (T1), en 4 maanden later (T2). De wachtlijstgroep werd op overeenkomstige momenten gemeten. 89% van de deelnemers rondde de T1 meting af, en 77% de T2 meting. 67% van de deelnemers uit de interventiegroep maakte de therapie af (3 of meer modules afgerond). Het versturen van sms ter aanmoediging en herinnering aan de cursus bleek niet significant bij te dragen aan het afmaken (65% met, versus 69% zonder sms).

Deelnemers uit beide groepen lieten een grote afname van depressieve klachten zien, maar er werd geen significant verschil gevonden tussen de interventie- en wachtlijstgroep op T1

(*d*=0,23; 95%BI=-0,17–0,63; *p*=0,259) of op T2 (*d*=0,01; 95%BI=-0,44–0,46; *p*=0,953). Ook degenen die de interventie hadden afgemaakt lieten geen verschil in daling van depressieve klachten zien op T1 (*d*=0,33; 95%BI=-0,11–0,77; *p*=0,136) of T2 (*d*=0,05; 95%BI=-0,43–0,53; *p*=0,828) vergeleken met de wachtlijstgroep. Op T1 werd een klinisch relevante verbetering (minimaal 5 punten BDI-II daling) waargenomen in depressieve klachten bij 66% van de interventiegroep en 53% van de wachtlijstgroep (*p*=0,087). Op T2 was dit het geval bij respectievelijk 63% versus 60% (*p*=0,743). Van de interventiegroep was 24% op T1 hersteld van depressieve klachten (BDI-II totaalscore<13 én minimaal 5 punten afname) versus 18% in de wachtlijstgroep, wat niet van elkaar verschilde (*p*=0,335). Op T2 was dit respectievelijk 28% versus 26% (*p*=0,722). Op secundaire uitkomstmaten, zoals angst, vermoeidheid en cognitief functioneren werden evenmin verschillen gevonden tussen beide groepen.

Geconcludeerd werd dat een probleemoplossende zelfhulp interventie via internet voor matig tot ernstig depressieve mensen met MS niet effectiever is dan plaatsing op een wachtlijst in het verminderen van depressieve klachten. Deze bevinding komt niet overeen met wat eerdere interventiestudies vonden voor (face-to-face) CGT bij depressieve mensen met MS, of CGT via internet bij depressieven mensen uit de algemene bevolking. Een vergelijkbare studie van een onderzoeksgroep in Duitsland vond recent wel succesvolle resultaten voor een CGT-interventie via internet bij mensen met MS met depressieve klachten vergeleken met een wachtlijstgroep. De substantiële afname van depressieve klachten in onze wachtlijstgroep was dan ook onverwacht en verschilt van die in bovengenoemde studies. Mogelijk hadden wij te maken met een zeer gemotiveerde subgroep (selectiebias) of met regressie naar het gemiddelde, waarbij ook zonder behandeling een terugkeer naar een minder depressieve toestand te verwachten is.

Vooralsnog is er geen reden om aan te nemen dat een psychologische interventie via internet niet waardevol kan zijn voor de behandeling van depressie bij mensen met MS, maar meer onderzoek is gewenst. Onderzoek zou zich kunnen richten op diverse of meer uitgebreide 'evidence-based'-behandelingen voor depressie waarbij ook gedacht kan worden aan een combinatie van behandeling via internet met 'face-to-face' behandeling (de zogenaamde 'blended'-behandeling) of een combinatie met medicatiebehandeling. Daarbij moet gekeken worden naar óf en hóe behandeling moet worden toegespitst op deze doelgroep en de aanwezigheid van MS, en wie kan profiteren van welke (online) therapie en in welke vorm (online begeleid, gemengd online/face-to-face, onbegeleid; al dan niet probleemoplossend) en intensiteit. Het is van belang zicht te krijgen op welke mensen baat hebben bij een wachtperiode alvorens eventueel behandeling te starten, welke mensen vervolgens voortijdig behandeling stoppen, in welke tijdsperiode en onder welke omstandigheden (hersteld, verslechterd, voldoende tevreden) en wat hierbij acceptabel is. Daarbij moet er rekening mee gehouden worden dat behandeling van depressie bij mensen met MS een grotere uitdaging kan zijn in vergelijking met behandeling van depressieve mensen zonder MS vanwege complexiteit door de aanwezigheid van een comorbide lichamelijke ziekte.

Ter afsluiting

In de aflopen jaren is steeds meer aandacht gekomen voor MS met co morbide depressie én voor moderne technologische ontwikkelingen in de behandeling van psychische problemen. De

combinatie van beide gebieden is dan ook een interessant en dynamisch onderzoeksveld. Dit proefschrift beoogt bij de dragen aan een betere herkenning en behandeling van depressie bij mensen met MS. Er zijn nog veel hordes te nemen, want het samengaan van beide aandoeningen is complex op veel verschillende niveaus. Ons begrip van de specifieke kenmerken van MS-gerelateerde depressie, indicaties voor psychologische behandelvormen, en interacties tussen patiëntvariabelen is nog onvolledig. Toekomstig onderzoek kan hierin beter inzicht geven, en zo hopelijk een bijdrage leveren aan een betere kwaliteit van leven voor mensen die te maken hebben met de chronische aandoening MS.

DANKWOORD

De afgelopen jaren heb ik met veel plezier aan mijn onderzoek gewerkt. Graag wil ik iedereen bedanken die daaraan heeft bijgedragen. Allereerst gaat veel dank uit naar alle mensen met MS die hebben meegedaan aan het onderzoek beschreven in dit proefschrift. Dankzij hun bereidwilligheid en inzet hebben we meer inzicht gekregen in de werkzaamheid van internet-therapie voor depressie bij mensen met MS, wat de toekomstige behandeling voor deze groep ten goede kan komen. Daarnaast is er een aantal personen dat ik graag bij naam noem.

Mijn promoter Patricia van Oppen. Beste Patricia, heel veel dank voor je ruimhartigheid, enorme vertrouwen en de kansen die je mij hebt geboden als onderzoeker én clinicus. Je deur stond altijd voor mij open en zowel op werk als daarbuiten hebben we veel plezier gehad. De combinatie van jouw klinische expertise en wetenschappelijke kennis was een bron van inspiratie en plaatste mijn onderzoek telkens weer in breder (patiënt)perspectief. Ik ben blij dat we deze combinatie van onderzoek en praktijk samen kunnen voortzetten. Jouw steun gedurende een voor mij zeer verdrietige periode zal ik nooit vergeten.

Mijn promotor Bernard Uitdehaag. Beste Bernard, wat een voorrecht om een neuroloog in mijn projectteam te hebben die zo veel weet van MS. Ik heb bewondering voor het gerenommeerde MS-centrum dat je leidt en waar ik altijd welkom was om aan te schuiven. Ik heb veel baat gehad bij je methodologische commentaar op mijn project en artikelen. In een mum van tijd wist je hoofd- en bijzaken van elkaar te scheiden en kwam je met toepasbare oplossingen. Veel dank voor de prettige samenwerking!

Mijn co-promotor Joost Dekker. Beste Joost, van jou kreeg ik altijd heel snel nauwgezette en constructieve feedback op vragen en conceptversies. Daarnaast heb ik jouw betrokkenheid bij de voortgang van het project afgelopen jaren erg gewaardeerd. We delen een interesse in de veerkacht van de mens. En wanneer mijn veerkracht gedurende dit traject weleens op de proef werd gesteld, bracht jij realiteitszin. In de toekomst hoop ik met jou de Soma&Psyche nog verder te ontwarren en samen te brengen.

Mijn co-promotor Aartjan Beekman. Beste Aartjan, in menigeen ontsteek jij het klinische vuur. Vanuit jouw enorme kennis over en ervaring met de wetenschap en psychiatrie, stelde jij vaak de belangrijke klinische vragen die een waardevolle aanvulling vormden op de reeds ingeslagen weg. Je daagde me uit om meer mijn eigen standpunten in te nemen. Veel dank hiervoor.

De leden van de promotiecommissie, prof.dr. O. van den Heuvel, prof.dr. H. Riper, prof.dr. R.Q. Hintzen, Dr. J.A. Knoop, Dr. D.J.F. van Schaik, en Dr. B.A. de Jong wil ik bedanken voor het beoordelen van dit proefschrift en het plaatsnemen in de oppositie.

Ook wil ik mijn co-auteurs bedanken. Brenda Penninx, wat was het inspirerend om met jou samen te werken; voor alles is een oplossing, een verklaring en weer een nieuwe vraag. Jan Smit, voor jou is geen berg te hoog. Behalve een mooi artikel kwam er toch alsnog een fMRI-subsidie en kunnen we ook nog in de toekomst blijven samenwerken. Heel veel dank hiervoor! Lenka, van jou nam ik het project over en ik ben je erkentelijk voor het uitvoeren van de pilotstudie en het voorwerk voor de trial. Beste Adriaan, dank voor je leuke lessen in de statistiek en je engelengeduld. Roxanne, wat ben jij een vrolijke en slimme collega en een tovenaar met synstaxbestan-

den bestanden. Pim Cuijpers, dank voor je hulp bij de meta-analyse. En natuurlijk Emma Collette, Vincent de Groot, Chris Polman en Kim Bakker van het MS centrum. Tot slot Annemarie: Wij beoordeelden niet alleen talloze artikelen samen voor het review, maar deelden ook lief en leed op congressen en in de tijd dat we naast elkaar in de gang 'woonden'. Dank voor het waarnemen bij mijn afwezigheid en fijn dat ik nog steeds bij je terecht kan voor je advies en gezelligheid.

Veel dank gaat uit naar Denise. Denise, jij nam het datamanagement op indrukwekkend consciëntieuze en gedegen wijze onder je hoede en verrichtte achter de schermen onmisbaar werk. Daarnaast kon ik met mijn 'technische' vragen altijd bij je terecht. Ook dank aan Gerard en Ho Ming hiervoor.

Graag wil ik ook diegenen bedanken die geholpen hebben bij de werving en verwijzing van respondenten. In het bijzonder Lisanne, Judith, Annette en Kim van het MS centrum van het VUmc. Kim was als MS-verpleegkundige bovendien onmisbaar voor de uitvoering van het screeningsproject. Voor dat project wil ik ook Vincent, Emma, Joep, Marja en Joke bedanken.

Nina, Sascha, Kim en Melany verrichtten samen met mij de klinische interviews en metingen, en begeleidden de interventies. Veel dank daarvoor! In het bijzonder Nina, dank voor je betrokkenheid en de bemoedigende woorden wanneer ik zo mijn twijfels had.

Carla, Rianne, Ineke, Reen, Claudia en Karin, dank voor al jullie ondersteuning bij het project gedurende de afgelopen jaren. Geweldig dat ik altijd zomaar kon binnen lopen!

In de jaren dat ik op de M-gang zat heb ik veel fijne collega's leren kennen die ik wil danken voor de motiverende en gezellige tijd die wij samen hebben gehad: Adrie (extra dank voor het me op weg helpen en houden), Annelies, Barbara, Carmilla, Catherine, Carisha, Claudia, Deborah, Dóra, Ellen, Hanna, Ilse B, Ilse W, Jet, Josine V, Josine v M, Judith, Laura, Lynn, Lisette, Lucas, Mandy, Nadien, Nienke, Nicole, Renske, Roxanne S, Roxanne G, Sascha, Sarah, Wendy, Wicher en Wouter. Onvergetelijke congressen beleefde ik met Mayke, Lisa, Willemijn, Merijn, en Henny. Dank ook aan alle post-docs, in het bijzonder Wouter en Arianne. Verder wil ik Lena bedanken, en Hanneke, Heleen en Quinten van 'Anatomie & Neurowetenschappen' voor de samenwerking en het fMRI onderzoek dat daaruit is voortgevloeid. Dank ook aan alle andere onderzoekers en collega's van de afdeling voor de collegialiteit.

Mijn supervisors, werkbegeleiders en collega's van de SOLK-poli en de depressie-poli wil ik bedanken voor hun interesse in mijn onderzoek tijdens mijn GZ-opleiding aldaar, evenals mijn GZ-opleidingsgenoten voor hun steun langs de zijlijn. Dank ook aan mijn huidige collega's van de eHealth@Mind poli; Ik verheug me op het blended-avontuur dat voor ons in het verschiet ligt.

Mijn paranimfen Jenneke en Anouk. Lieve Jenneke, vanaf dag één was jij voor mij een reuze aanwinst en zeker niet alleen omdat je een soortgelijk combinatie-traject had doorlopen. Ik word altijd weer vrolijk als je je hoofd om mijn kamerdeur steekt met je kannetje thee. Wat een geluk om de afgelopen jaren van alles met elkaar te hebben kunnen delen. Lieve Nouk, waar een werkgroep psychologie al niet goed voor is: vriendschap op het eerste gezicht werd vriendschap voor het leven. Naast elkaar wonen en werken. 'Groots en meeslopend' durf ik wel met jou. 'You are my silver lining' en nog heel veel meer.

Lieve vriendin Sophie(Ontwerpt//), heel veel dank voor (alle 14 versies van) de mooie cover!

Immer voel ik mij op de achtergrond gesterkt door mijn dierbare vrienden en (schoon-) familie. Mijn 'Zwitserse' familie wil ik in het bijzonder danken voor hun hartelijkheid in de tijd dat Steve en ik in Zürich verbleven. Jullie ruimdenkendheid is voor mij nastrevenswaardig! Mijn oma Lies wil ik hier vermelden als belangrijke vrouwelijke inspiratiebron. Lieve oma, bij de uitdagingen die het leven met zich meebrengt, blijf jij veerkrachtig en nieuwsgierig, en ga je mee met je (digitale) tijd. Ik ben trots op mijn broer Matthijs en zus Joanne (met Soof, Daan en de kleine Djuna!). Jullie zijn voor mij ongelooflijk belangrijk en blijven mij herinneren aan wie ik ben en wil zijn. Lieve pap en mam, ik ben jullie onbeschrijflijk dankbaar voor al jullie liefde, relativering en immer veilige haven om naar terug te keren. Tot slot, Steven, grote geliefde, dank voor je eindeloze geduld, vertrouwen en originaliteit: Jij bent verreweg het mooiste wat mij is overkomen.

CURRICULUM VITAE

Rosa Elisabeth Boeschoten was born on July 1, 1983 in Hilversum, the Netherlands, where she finished high school at the Gemeentelijk Gymnasium in 2001. Hereafter she studied Italian for seven months in Rome and Siena, Italy. In 2002 Rosa started studying Psychology at the University of Amsterdam (UvA). She obtained a Bachelor's degree 'Cum Laude' in Cognitive Psychology in 2005, and graduated 'Cum Laude' with Master's degrees in Social Psychology (2007) and Clinical Psychology (2010). During her Master she participated for six months in the PhD research program at the Psychology department of the New York University, (2006). She also accomplished the Master track 'Training and Development' at the UvA in 2008. From September 2008 until February 2009 she worked as a student-assistant to prof.dr. M. Kindt in the department of Experimental Clinical Psychology. From September 2008 until March 2010 she lectured part-time at the Psychology Department of the UvA, developing and teaching seminars for undergraduates.

In October 2010 Rosa started her PhD at the research department of GGZ inGeest and the department of Psychiatry of the VU University Medical Center (VUmc) in Amsterdam, which resulted in this thesis. From 2012 until 2015 she combined her PhD research with a postdoctoral training program to become a licensed mental health care psychologist ('GZ-psycholoog'), and worked at the outpatient clinic for medically unexplained disorders of the VUmc and at the depression outpatient clinic of GGZ inGeest. Rosa now continues her research at GGZ inGeest and the VUmc, and works as a mental health psychologist at the E-mental health clinic of GGZ inGeest.

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